Method of Inhibiting Protein Tyrosine Phosphatase 1B and/or T-cell Protein Tyrosine Phosphatase and/or other PTPases with an Asp Residue at Position 48

> This application claims the benefit of U.S. Prov. Appl. 60/156,641, filed 09/29/99.

Field of the Invention

This invention relates to a method of inhibiting Protein Tyrosine Phosphatase 1B (PTP1B) and/or T-cell Protein Tyrosine Phosphatase (TC-PTP) and/or Protein Tyrosine Phosphatases (PTPases) having an aspartic acid (Asp) in position 48 (PTP1B numbering, Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)) by exposing such an enzyme to inhibitor compounds, i.e., to compounds possessing certain structural, physico-chemical and spatial characteristics that allow them to interact with specific amino acid residues of the active site (and the vicinity of the active site) of PTP1B and/or TC-PTP and more generally Protein Tyrosine Phosphatases (PTPases) having an aspartic acid (Asp) in position 48. The resulting inhibition of the PTPase enzymatic activity makes these compounds useful for elucidating the function of PTP's e.g., by inhibiting a PTP and observing up-or down-regulation of other proteins. Additionally, such inihibitors serve as early development candidates, development candidates, or prototype drugs for treatment of or paliation of diseases and dysfunctions such as diabetes type I and II and obesity, cancer, immune disorders (including allergy and abnormal autoimmunity), and conditions involving disturbances in platelet aggregation as well as infectious diseases. This invention also relates to (I) the design and selection of inhibitors which bind to the active site of PTP1B and/or TC-PTP and/or PTPases having an aspartic acid (Asp) in position 48 (II) the synthesis of said inhibitors, methods for their preparation and (III) to compositions comprising the inhibitor compounds.

Background of the Invention

Protein phosphorylation is now well recognized as an important mechanism utilized by cells to transduce and regulate signals during different stages of cellular function (Hunter, *Phil. Trans. R. Soc. Lond.* B

353: 583-605 (1998); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Zhang, *Curr. Top. Cell. Reg. 35*: 21-68 (1997); Matozaki and Kasuga, *Cell. Signal. 8*: 113-19 (1996); Fischer *et al, Science 253*:401-6 (1991); Flint *et al., EMBO J. 12*:1937-46 (1993)). The level of tyrosine phosphorylation is balanced by the opposing action of protein tyrosine kinases and protein tyrosine phosphatases. There are at least two major classes of phosphatases: (1) those that dephosphorylate proteins (or peptides) that contain a phosphate group(s) on a serine or threonine moiety (termed Ser/Thr phosphatases) and (2) those that remove a phosphate group(s) from the amino acid tyrosine (termed protein tyrosine phosphatases or PTPases or PTPs).

The PTPases are a family of enzymes that can be classified into two groups: a) intracellular or nontransmembrane PTPases and b) receptor-type or transmembrane PTPases. In addition, dual-specificity phosphatases and low molecular weight phosphatases are able to dephosphorylate phospho tyrosyl proteins. See, e.g., WO 97/ 39746; WO 97/ 40017; WO 99/ 15529; WO 97/08934; WO 98/ 27065; WO 99/46236; WO 99/46244; WO 99/46267; WO 99/46268 and WO 99/46237.

Intracellular PTPases: Most known intracellular type PTPases contain a single conserved catalytic phosphatase domain consisting of 220-240 amino acid residues. The regions outside the PTPase domains are believed to play important roles in localizing the intracellular PTPases subcellularly (Mauro, L.J. and Dixon, J.E. *TIBS 19*: 151-155 (1994)). The first intracellular PTPase to be purified and characterized was **PTP1B**, which was isolated from human placenta (Tonks *et al., J. Biol. Chem. 263*: 6722-6730 (1988)). Shortly after, PTP1B was expressed recombinantly (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989); Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)). Other examples of intracellular PTPases include (1) **T-cell PTPase/ TC-PTP** (Cool *et al. Proc. Natl. Acad. Sci. USA 86*: 5257-5261 (1989)), (2) **rat brain PTPase** (Guan *et al., Proc. Natl. Acad. Sci. USA 87*:1501-1502 (1990)), (3) neuronal

several different members of the receptor-type PTPase group. Thus, 5 different PTPases, (3) **PTPα,** (4) **PTPβ,** (5) **PTPδ,** (6) **PTPε,** and (7) **PTPζ,** were identified in one early study (Krueger *et al., EMBO J. 9*: 3241-3252 (1990)). Other examples of receptor-type PTPases include (8) **PTPγ** (Barnea *et al., Mol. Cell. Biol. 13*: 1497-1506 (1995)) which, like **PTPζ** (Krueger and Saito, *Proc. Natl. Acad. Sci. USA 89*: 7417-7421 (1992)) contains a carbonic anhydrase-like domain in the extracellular region, (9) **PTPμ** (Gebbink *et al., FEBS Letters 290*: 123-130 (1991)), (10) **PTPκ** (Jiang *et al., Mol. Cell. Biol. 13*: 2942-2951 (1993)). Based on structural differences the receptor-type PTPases may be classified into subtypes (Fischer *et al., Science 253*: 401-406 (1991)): (I) CD45; (II) LAR, PTPd, (11) **PTPσ** ; (III) **PTPβ**, (12) **SAP-1** (Matozaki *et al., J. Biol. Chem. 269*: 2075-2081 (1994)), (13) **PTP-U2/GLEPP1** (Seimiya *et al., Oncogene 10*: 1731-1738 (1995); Thomas *et al., J. Biol. Chem. 269*: 19953-19962 (1994)), and (14) **DEP-1**; (IV) **PTPα, PTPε**. All receptor-type PTPases except Type III contain two PTPase domains. Novel PTPases are frequently identified, and it is anticipated that between 100 and more than 500 different species will be found in the human genome.

PTPases are the biological counterparts to protein tyrosine kinases (PTKs). Therefore, one important function of PTPases is to control, and especially down-regulate, the activity of PTKs. However, a more complex picture of the function of PTPases has emerged. Thus, several studies indicate that some PTPases act as positive mediators of cellular signaling. As an example, the SH2 domain-containing SHP-2 acts as a positive mediator in insulin-stimulated Ras activation (Noguchi *et al., Mol. Cell. Biol. 14*: 6674-6682 (1994)) and of growth factor-induced mitogenic signal transduction (Xiao *et al., J. Biol. Chem. 269*: 21244-21248 (1994)), whereas the homologous SHP-1 acts as a negative regulator of growth factor-stimulated proliferation (Bignon and Siminovitch, *Clin.Immunol. Immunopathol. 73*: 168-179 (1994)). Another example of PTPases as positive regulators has been provided by studies designed to define the activation of the Src-family of tyrosine

kinases. In particular, several lines of evidence indicate that CD45 is positively regulating the activation of hematopoietic cells, and that the mechanism of such positive regulation may involve dephosphorylation of the C-terminal tyrosine of Fyn and Lck (Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994)).

The association of many PTPases with cell proliferation, tranformation and differentiation has now been established. PTP1B, a phosphatase whose structure was the first PTPase to be elucidated (Barford *et al., Science* 263:1397-1404 (1994)) has been shown to be involved in insulin-induced oocyte maturation (Flint *et al., The EMBO J.* 12:1937-46 (1993)) and the overexpression of this enzyme has been implicated in $p185^{c\text{-}erb\ B2}$-associated breast and ovarian cancers (Weiner, *et al., J. Natl. cancer Inst.* 86:372-8 (1994); Weiner *et al., Am. J. Obstet. Gynecol.* 170:1177-883 (1994)). The association with cancer is on the basis of evidence that overexpression of PTP1B is statistically correlated with increased levels of $p185^{c\text{-}erb\ B2}$ in ovarian and breast cancer. The role of PTP1B in the etiology and progression of the disease has not yet been elucidated. Inhibitors of PTP1B therefore would help clarify the role of PTP1B in cancer and in some cases provide therapeutic treatment for certain forms of cancer.

<u>PTPases: the insulin receptor signaling pathway/diabetes</u>

Insulin is an important regulator of different metabolic processes and plays a key role in the control of blood glucose. Defects related to its synthesis or signaling lead to diabetes mellitus. Binding of insulin to the insulin receptor (IR) causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the β-subunit. Three closely positioned tyrosine residues (the tyrosine-1150 domain) must all be phosphorylated to obtain full activity of the insulin receptor tyrosine kinase (IRTK) which transmits the signal further downstream by tyrosine phosphorylation of other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden *et al., J. Biol. Chem. 267*: 16660-16668 (1992); Myers and White, *Diabetes 42*: 643-650 (1993); Lee and

Pilch, *Am. J. Physiol. 266*: C319-C334 (1994); White *et al., J. Biol. Chem. 263*: 2969-2980 (1988)). The structural basis for the function of the tyrosine-triplet has been provided by X-ray crystallographic studies of IRTK that showed the tyrosine-1150 domain to be autoinhibitory in its unphosphorylated state (Hubbard *et al., Nature 372*: 746-754 (1994)) and of the activated IRTK (Hubbard, *EMBO J.* 16: 5572-5581 (1997)).

Several studies clearly indicate that the activity of the auto-phosphorylated IRTK can be reversed by dephosphorylation *in vitro* (reviewed in Goldstein, *Receptor 3*: 1-15 (1993); Mooney and Anderson, *J. Biol. Chem. 264*: 6850-6857 (1989)), with the tri-phosphorylated tyrosine-1150 domain being the most sensitive target for protein-tyrosine phosphatases (PTPases) as compared to the di- and mono- phosphorylated forms (King *et al., Biochem. J. 275*: 413-418 (1991)). This tyrosine-triplet functions as a control switch of IRTK activity and IRTK appears to be tightly regulated by PTP-mediated dephosphorylation *in vivo* (Khan *et al., J. Biol. Chem. 264*: 12931-12940 (1989); Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992); Rothenberg *et al., J. Biol. Chem. 266*: 8302-8311 (1991)). The intimate coupling of PTPases to the insulin signaling pathway is further evidenced by the finding that insulin differentially regulates PTPase activity in rat hepatoma cells (Meyerovitch *et al., Biochemistry 31*: 10338-10344 (1992)) and in livers from alloxan diabetic rats (Boylan *et al., J. Clin. Invest. 90*: 174-179 (1992)).

Until recently, relatively little was known about the identity of the PTPases involved in IRTK regulation. However, the existence of PTPases with activity towards the insulin receptor can be demonstrated as indicated above. Further, when the strong PTPase-inhibitor pervanadate is added to whole cells an almost full insulin response can be obtained in adipocytes (Fantus *et al.*, *Biochemistry 28*: 8864-8871 (1989); Eriksson *et al.*, *Diabetologia 39*: 235-242 (1995)) and skeletal muscle (Leighton *et al.*, *Biochem. J. 276*: 289-292 (1991)). In addition, other studies show that a new class of peroxovanadium compounds act as potent hypoglycemic compounds *in vivo* (Posner *et al.,supra*). Two

of these compounds were demonstrated to be more potent inhibitors of dephosphorylation of the insulin receptor than of the EGF-receptor, thus indicating that even such relatively unselective inhibitors may show some specificity in regulating different signal transduction pathways.

It was recently found that mice lacking the protein tyrosine phosphatase-1B gene (PTP1B) (Elchebly *et al.*, *Science 283:* 1544-1548 (1999)) yielded healthy mice thatshowed increased insulin sensitivity and were resistant to diet-induced obesity. These results were confirmed by Kaman at al *Mol. Cell Biol.* 20:5479-5489 (2000).The enhanced insulin sensitivity of the PTP$^{-/-}$ mice was also evident in glucose and insulin tolerance tests.

The PTP-1B knock-out mouse showed many characteristics which would be highly desirable results for an anti-diabetes treatment. Most importantly, the knock-out mice grew normally and were fertile and have exhibited no increased incidence of cancer. Blood glucose and insulin levels were lowered, and insulin sensitivity increased. Moreover, the insulin-stimulated tyrosine phosphorylation levels of IR and IRS-1 were found to be increased/prolonged in muscle and liver – but not in fat tissue. Thus, the main target tissues for this type of approach would appear to be insulin action in liver and muscle.

Several other "diabetic" parameters were also improved, including plasma triglycerides which were decreased in the knock-out mice. The knock-animals also exhibited a resistance to weight gain when placed on a high-fat diet. This is in contrast to the action of the PPARγ agonist class of insulin sensitizers, which rather induce weight gain (Murphy & Nolan, *Exp. Opin. Invest. Drugs* 9:1347-1361, 2000), and would suggest that inhibition of PTP-1B could be a particularly attractive option for treatment of obese Type II diabetics.

This is also supported by the fact that the heterozygous mice from this study showed many of these desirable features. The reduction in weight gain of the knock-out animals on the high fat diet was found to be due to a decreased fat cell mass, although differences were observed with respect to fat cell number. Leptin levels were also lower in the knock-out

mice, presumably as a reflection of the decreased fat mass. Significantly, the Klaman et al group also found that the knock-out animals had an increased energy expenditure of around 20% and an increased respiratory quotient compared to the wild-type; again, heterozygote animals displayed an intermediate level of energy expenditure. Therefore, inhibition of this enzyme may be an effective anti-diabetic and perhaps also anti-obesity therapy .

It should also be noted that in the PTP-1B knock-out mice the basal tyrosine phosphorylation level of the insulin receptor tyrosine kinase does not appear to be increased, which is in contrast to the situation after insulin treatment where there is an increased or prolonged phosphorylation. This might indicate that other PTPs are controlling the basic phosphorylation state of the insulin receptor in the knock-out mice – and is expected to do so in man.

Also other PTPases have been implicated as regulators of the insulin signaling pathway. Thus, it was found that the ubiquitously expressed SH2 domain containing PTPase, PTP1D/SHP-2 (Vogel *et al.*, 1993, *supra*), associates with and dephosphorylates IRS-1, but apparently not the IR itself (Kuhné *et al., J. Biol. Chem. 268*: 11479-11481 (1993); (Kuhné *et al., J. Biol. Chem. 269*: 15833-15837 (1994)).

Other studies suggest that receptor-type or membrane-associated PTPases are involved in IRTK regulation (Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992), (Häring *et al., Biochemistry 23*: 3298-3306 (1984); Sale, *Adv. Prot. Phosphatases 6*: 159-186 (1991)).

While previous reports indicate a role of PTPα in signal transduction through src activation (Zheng *et al., Nature 359*: 336-339 (1992); den Hertog *et al., EMBO J. 12*: 3789-3798 (1993)) and interaction with GRB-2 (den Hertog *et al., EMBO J. 13*: 3020-3032 (1994); Su *et al., J. Biol. Chem. 269*: 18731-18734 (1994)), Møller, Lammers and coworkers provided results that suggest a function for this phosphatase and its close relative PTPε as negative regulators of the insulin receptor signal (Møller *et al.*, 1995 *supra*;

Lammers, *et al.* , *FEBS Lett.* 404:37-40 (1997). These studies also indicated that receptor-like PTPases may play a significant role in regulating the IRTK, including through direct influence on the insulin receptor itself.

Other studies have shown that PTP1B and TC-PTP are likely to be involved in the regulation of several other cellular processes in addition to the described regulatory roles in insulin signaling. Therefore, PTP1B and/or TC-PTP as well as other PTPases showing key structural features with PTP1B and TC-PTP are likely to be important therapeutic targets in a variety of human and animal diseases. The compounds of the present invention are useful for modulating or inhibiting PTP1B and/or TC-PTP and/or other PTPases showing key structural features with said PTPases and thus elucidating their function and for treating disease states in which said modulation or inhibition is indicated.

Further, PTPases influence the following hormones or diseases or disease states: somatostatin, the immune system/autoimmunity, cell-cell interactions/cancer, platelet aggregation, osteoporosis, and microorganisms, as disclosed in PCT Publication WO 99/15529.

PTPases: the immune system/autoimmunity

Several studies suggest that the receptor-type PTPase CD45 plays a critical role not only for initiation of T cell activation, but also for maintaining the T cell receptor-mediated signaling cascade. These studies are reviewed in: (Weiss A., *Ann. Rev. Genet. 25*: 487-510 (1991); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Trowbridge and Thomas, *Annu. Rev. Immunol. 12*: 85-116 (1994)).

CD45 is one of the most abundant of the cell surface glycoproteins and is expressed exclusively on hemopoetic cells. In T cells, it has been shown that CD45 is one of the critical components of the signal transduction machinery of lymphocytes. In particular, there is evidence that CD45 phosphatase plays a pivotal role in antigen-stimulated proliferation of T lymphocytes after an antigen has bound to the T cell receptor (Trowbridge, *Ann. Rev. Immunol*, 12: 85-116 (1994)). Several studies indicate that the PTPase activity of CD45 plays a role in the

activation of Lck, a lymphocyte-specific member of the Src family protein-tyrosine kinase (Mustelin etal., *Proc. Natl. Acad. Sci. USA 86*: 6302-6306 (1989); Ostergaard *et al., Proc. Natl. Acad. Sci. USA 86*: 8959-8963 (1989)). Studies using transgenic mice with a mutation for the CD45-exon6 exhibited a lack of mature T cells. These mice did not respond to an antigenic challenge with the typical T cell mediated response (Kishihara *et al.*, *Cell 74*:143-56 (1993)). Inhibitors of CD45 phosphatase would therefore be very effective therapeutic agents in conditions that are associated with autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, and inflammatory bowel disease. Another important function of CD45 phosphatase inhibitors is in effecting immunosuppression, where such a result is indicated, e.g., in transplantation and other conditions in need of immunosuppressive treatment.

CD45 has also been shown to be essential for the antibody mediated degranulation of mast cells (Berger *et* al., *J. Exp. Med. 180*:471-6 (1994)). These studies were also done with mice that were CD45-deficient. In this case, an IgE-mediated degranulation was demonstrated in wild type but not CD45-deficient T cells from mice. These data suggest that CD45 inhibitors could also play a role in the symptomatic or therapeutic treatment of allergic disorders, such as asthma, allergic rhinitis, food allergies, eczema, urticaria and anaphylaxis. Another PTPase, an inducible lymphoid-specific protein tyrosine phosphatase (HePTP) has also been implicated in the immune response. This phosphatase is expressed in both resting T and B lymphocytes, but not non-hemopoetic cells. Upon stimulation of these cells, mRNA levels from the HePTP gene increase 10-15 fold (Zanke *et al., Eur. J. Immunol. 22*: 235-239 (1992)).

Likewise, the hematopoietic cell specific SHP-1 acts as a negative regulator and thus appears to play an essential role in immune cell development.In accordance with the above-mentioned important function of CD45, HePTP and SHP-1, selective PTPase inhibitors are early development candidates or prototype drugs both as immunosuppressors and as immunostimulants. Recent studies illustrate the potential of

PTPase inhibitors as immunmodulators by demonstrating the capacity of the vanadium-based relatively nonselective PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven *et al.*, *J. Biol. Chem. 270*: 20824-20831 (1995)).

PTPases: cell-cell interactions/cancer

Focal adhesion plaques, an *in vitro* phenomenon in which specific contact points are formed when fibroblasts grow on appropriate substrates, mimic, in certain respects, cells and their natural surroundings. Several focal adhesion proteins are phosphorylated on tyrosine residues when fibroblasts adhere to and spread on extracellular matrix (Gumbiner, *Neuron 11:* 551-564 (1993)). However, aberrant tyrosine phosphorylation of these proteins can lead to cellular transformation. The intimate association between PTPases and focal adhesions is supported by the finding of several intracellular PTPases with ezrin-like N-terminal domains, e.g. PTPMEG1 (Gu *et al., Proc. Natl. Acad. Sci. USA 88*: 5867-5871 (1991), PTPH1 (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)) and PTPD1 (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)). The ezrin-like domains show similarity to several proteins that are believed to act as links between the cell membrane and the cytoskeleton. PTPD1 was found to be phosphorylated by and associated with c-src *in vitro* and is hypothesized to be involved in the regulation of phosphorylation of focal adhesions (Møller *et al.*, *supra*).

PTPases may oppose the action of tyrosine kinases, including those responsible for phosphorylation of focal adhesion proteins, and may therefore function as natural inhibitors of transformation. TC-PTP, and especially the truncated form of this enzyme (Cool *et al., Proc. Natl. Acad. Sci. USA 87:* 7280-7284 (1990)), can inhibit the transforming activity of v-*erb* and v-*fms* (Lammers *et al., J. Biol. Chem. 268:* 22456-22462 (1993), Zander *et al., Oncogene 8:* 1175-1182 (1993)). Moreover, it was found that transformation by the oncogenic form of the *HER2/neu* gene was suppressed in NIH 3T3 fibroblasts

overexpressing PTP1B (Brown-Shimer *et al., Cancer Res. 52:* 478-482 (1992)).

The expression level of PTP1B was found to be increased in a mammary cell line transformed with *neu* (Zhay *et al., Cancer Res. 53:* 2272-2278 (1993)). The intimate relationship between tyrosine kinases and PTPases in the development of cancer is further evidenced by the recent finding that PTPe is highly expressed in murine mammary tumors in transgenic mice over-expressing c-*neu* and v-Ha-*ras*, but not c-*myc* or *int-2* (Elson and Leder, *J. Biol. Chem. 270:* 26116-26122 (1995)). Further, the human gene encoding PTPγ was mapped to 3p21, a chromosomal region which is frequently deleted in renal and lung carcinomas (LaForgia *et al., Proc. Natl. Acad. Sci. USA 88*: 5036-5040 (1991)).

PTPases appear to be involved in controlling the growth of fibroblasts. In a recent study it was found that Swiss 3T3 cells harvested at high density contain a membrane-associated PTPase whose activity on an average is 8-fold higher than that of cells harvested at low or medium density (Pallen and Tong, *Proc. Natl. Acad. Sci. USA 88*: 6996-7000 (1991)).

Two closely related receptor-type PTPases, PTPκ and PTPμ, can mediate homophilic cell-cell interaction when expressed in non-adherent insect cells, suggesting that a normal physiological function for these PTPases in cell-to-cell signalling (Gebbink *et al., J. Biol. Chem. 268*: 16101-16104 (1993), Brady-Kalnay *et al., J. Cell Biol. 122*: 961-972 (1993); Sap *et al., Mol. Cell. Biol. 14*: 1-9 (1994)). Interestingly, PTPκ and PTPμ do not bind to each other (PTPκ does self-associate), despite their structural similarity (Zondag *et al., J. Biol. Chem. 270*: 14247-14250 (1995)).

From the studies described above it is apparent that PTPases play an important role in regulating normal cell growth. Additionally, as pointed out above, PTPases may also function as positive mediators of intracellular signaling and thereby induce or enhance mitogenic responses. Increased activity of certain PTPases might therefore result

in cellular transformation and tumor formation. *See*, Zheng, *supra*; Uchida *et al., J. Biol. Chem. 269*: 12220-12228 (1994 Hunter, *Cell 80*: 225-236 (1995). Inhibitors of specific PTPases are therefore likely to be of significant therapeutic value in the treatment of certain forms of cancer.

PTPases: platelet aggregation

PTPases are centrally involved in platelet aggregation. Thus, agonist-induced platelet activation results in calpain-catalyzed cleavage of PTP1B with a concomitant 2-fold stimulation of PTPase activity (Frangioni *et al., EMBO J. 12:* 4843-4856 (1993)). The cleavage of PTP1B leads to subcellular relocation of the enzyme and correlates with the transition from reversible to irreversible platelet aggregation in platelet-rich plasma. In addition, the SH2 domain containing PTPase, SHP-1, was found to translocate to the cytoskeleton in platelets after thrombin stimulation in an aggregation-dependent manner (Li *et al., FEBS Lett. 343:* 89-93 (1994)).

Although some details in the above two studies have been questioned, there is overall agreement that PTP1B and SHP-1 play significant functional roles in platelet aggregation (Ezumi *et al., J. Biol. Chem. 270:* 11927-11934 (1995)). In accordance with these observations, treatment of platelets with the PTPase inhibitor pervanadate leads to significant increase in tyrosine phosphorylation, secretion and aggregation (Pumiglia *et al., Biochem. J. 286:* 441-449 (1992)).

PTPases: osteoporosis

The rate of bone formation is determined by the number and the activity of osteoblasts. In turn, these aredetermined by the rate of proliferation and differentiation of osteoblast progenitor cells, respectively. Histomorphometric studies indicate that the osteoblast number is the primary determinant of the rate of bone formation in humans (Gruber *et al., Mineral Electrolyte Metab. 12*: 246-254 (1987), reviewed in Lau *et al., Biochem. J. 257*: 23-36 (1989)). Acid

phosphatases/PTPases are implicated in negative regulation of osteoblast proliferation. Thus, fluoride, which has phosphatase inhibitory activity, has been found to increase spinal bone density in osteoporotics by increasing osteoblast proliferation (Lau *et al.*, *supra*). Consistent with this observation, an osteoblastic acid phosphatase with PTPase activity was found to be highly sensitive to mitogenic concentrations of fluoride (Lau *et al., J. Biol. Chem. 260*: 4653-4660 (1985), Lau *et al., J. Biol. Chem. 262*: 1389-1397 (1987), Lau *et al., Adv. Protein Phosphatases 4*: 165-198 (1987)). The mitogenic action of fluoride and other phosphatase inhibitors (molybdate and vanadate) may thus be explained by their inhibition of acid phosphatases/PTPases that negatively regulate the cell proliferation of osteoblasts. The complex nature of the involvement of PTPases in bone formation is further suggested by the recent identification of a novel parathyroid regulated, receptor-like PTPase, OST-PTP, expressed in bone and testis (Mauro *et al., J. Biol. Chem. 269*: 30659-30667 (1994)). OST-PTP is up-regulated following differentiation and matrix formation of primary osteoblasts and subsequently down-regulated in the osteoblasts which are actively mineralizing bone in culture. In addition, it was recently observed that vanadate, vanadyl and pervanadate all increased the growth of the osteoblast-like cell line UMR106. Vanadyl and pervanadate were stronger stimulators of cell growth than vanadate. Only vanadate was able to regulate the cell differentiation as measured by cell alkaline phosphatase activity (Cortizo *et al., Mol. Cell. Biochem. 145*: 97-102 (1995)). More important, several studies have shown that biphosphonates, such as alendronate and tiludronate, inhibit PTPase activity in osteoclasts and that the inhibition of PTPase activity correlated with the inhibition of *in vitro* osteoclast formation and bone resorption.(Scmidt, et al., *Proc. Natl Acad. Sci. U.S.A. 93*: 3068-3073,1996; Murakami et al., *Bone 20*:399-404, 1997; Opas et al., *Biochem. Pharmacol. 54*: 721-727, 1997; Skorey et al., *J. Biol. Chem. 272*: 22472-22480, 1997. Thus, other PTPase inhibitors are potentially effective in countering osteoclast activity, and thus treating osteoporosis.

PTPases: microorganisms

Dixon and coworkers have called attention to the fact that PTPases may be a key element in the pathogenic properties of *Yersinia* (reviewed in Clemens *et al. Molecular Microbiology 5*: 2617-2620 (1991)). This finding was rather surprising since tyrosine phosphate is thought to be absent in bacteria. The genus *Yersinia* comprises 3 species: *Y. pestis* (responsible for the bubonic plague), *Y. pseudoturberculosis* and *Y. enterocolitica* (causing enteritis and mesenteric lymphadenitis). A dual-specificity phosphatase, VH1, has been identified in Vaccinia virus (Guan *et al., Nature 350*: 359-263 (1991)). These observations indicate that PTPases may play critical roles in microbial and parasitic infections, and they further point to PTPase inhibitors as a novel, putative treatment principle of infectious diseases. Availibility of PTPase inhibitors would help shed light in all the foregoing specualations about PTPase function because they would enable assaying techniques which would answer some of these questions as will be illustrated below.

Summary of Background

It has been found that PTPases play a major role in the above modulation and regulation of fundamental cellular signaling mechanisms involved in metabolism, growth, proliferation and differentiation (Fisher *et al*, *Science* 253:401-6 (1991); Tonks and Neel, *Cell* 87: 365-368 (1966)" Neel and Tonks, *Current Opinion in Cell Biology* 9: 193-204 (1997); Hunter, *Phil. Trans. R. Soc. Lond. B* 353: 583-605 (1998); Hunter, *Cell* 100: 113-120 (2000); Zhang, *Critical Reviews in Biochemistry and Molecular Biology* 33:1-52 (1988)). Reports from many laboratories have shown that PTPases can act both as positive and negative regulators of signal transduction processes. PTPases have been implicated in a variety of human diseases, including diabetes, obesity, autoimmune diseases, acute and chronic inflammation, osteoporosis, proliferative disorders including various forms of cancer, growth disorders, and defective platelet

aggregation (WO97/39748, WO97/40017, WO99/1529, WO97/08934, WO98/27065, WO99/46236, WO99/46244, WO99/46267, WO99/46268, WO99/46237). Accordingly there is increasing evidence which suggests that inhibition of these PTPases would help treat or manage these diseases (Hunter, *vide supra*; Neel and Tonks, *vide supra*: Frangione et al., *EMBO J.* 12:4843-4856 (1993); Zhang, *Curr. Top. Cell. Reg.* 35. 21-68 (1997): Zhang, *vide supra*; Evans and Jalian, *Exp. Opinion. Invest. Drugs* 8: 139-160 (1999); Burke and Zhang, *Bioploymers (Peptide Science)* 47: 225-241 (1998): Elchebly *et al.*; *Science* 283: 1544-1548 (1999); Wrobel et al., *J. Med. Chem.* 42: 3199-3202 (1999)). In addition, certain infectious diseases may also be treated or managed by administration PTPase inhibitors (Clemens *et al., Molecular Microbiology* 5: 2617-2620 (1991)).

Both selective PTPase inhibitors and inhibitors that bind to several PTPases (non-selective inhibitors) can be used therapeutically to partially or completely restore PTPase-mediated perturbed signal transduction processes and thus for management, treatment, palliation or prevention of the above diseases.

Description of Drawings

Figure 1. Active site of Protein Tyrosine Phosphatase 1B complexed with with 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid.

Figure 2. Active site of Protein Tyrosine Phosphatase 1B complexed with 7-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (Example 26).

Figure 3. Active site of Protein Tyrosine Phosphatase 1B complexed with 5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (Example 4).

Figure 4. Active site of Protein Tyrosine Phosphatase 1B complexed with 2-(oxalyl-amino)-7-(1,1,3-trioxo-1H-benzo[d]isothiazol-3-yloxomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (Example 54). Selected water molecules are shown.

Description of the Invention

The present invention provides a method for inhibiting protein tyrosine phosphatase 1B (PTP1B) and/or T-cell protein tyrosine phosphatase (T-cell PTP/TC-PTP) and/or protein tyrosine phosphatases (PTPases) having an aspartic acid (Asp) in position 48 by exposing said PTPase to a compound having physico-chemical and spatial structural characteristics that interfere with the active site and/or vicinity of the active site of said PTPase thereby inhibiting its enzymatic activity. Specifically, the present inhibitors of PTP1B and/or TC-PTP and/or PTPases having an aspartic acid (Asp) in position 48 interact with two or more residues of the following: arginine 221, glycine 220, lysine 120, tyrosine 46, and phenylalanine/histidine 182 and one or more of the following (residue numbering correspondingto PTP1B will be used through out (Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)):

1. Isoleucine 219 backbone amide nitrogen;
2. Glycine 218 backbone amide nitrogen;
3. Alanine 217 backbone amide nitrogen ;
4. Serine 216 backbone amide nitrogen;
5. Cysteine 215 backbone amide nitrogen;
6. The side chain carboxylic acid group of aspartic acid 181;
7. The side chain carboxylic acid group of aspartic acid 48;
8. The side chain guanidinium group of arginine 47;
9. Arginine 47 backbone amide nitrogen;
10. Aspartic acid 48 backbone amide nitrogen;
11. The side chain hydroxy group of tyrosine 46;
12. The side chain amino group of lysine 41;
13. The methylene side chain atoms of lysine 41;
14. The backbone amide carbonyl of asparagine 44;
15. The methylene side chain atoms of arginine 45;

16. The backbone amide carbonyl of arginine 45;
17. The methylene side chain atoms of arginine 47;
18. The methylene side chain atom of aspartic acid 48;
19. The backbone amide carbonyl of aspartic acid 48;
20. The methylene side chain atoms of leucine 88;
21. The side chain hydroxy group of serine 118;
22. The backbone amide carbonyl of leucine 119;
23. The side chain amide nitrogen of glutamine 262;
24. The side chain atoms of methionine 258;
25. The aromatic group of phenylalanine 52;
26. The backbone amide nitrogen of glycine 259;
27. The alpha-methylene atom of glycine 259;
28. The guanidinium group of arginine 254;
29. The methylene side chain atoms of arginine 254;
30. The methylene side chain atoms of arginine 24;
31. The guanidinium group of arginine 24; or
32. Any conserved water molecule in the vicinity of the active site.

Preferably, the present inhibitors of PTP1B and/or TC-PTP and/or PTPases having an aspartic acid (Asp) in position 48 interact with any three or more of the above identified regions of the active site and its vicinity.

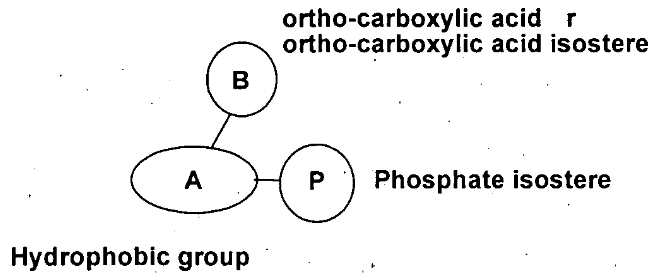
In one preference, the inhibitors of PTP1B and/or TC-PTP and/or PTPases having an aspartic acid (Asp) in position 48 interact with arginine 221, glycine 220, lysine 120, tyrosine 46, phenylalanine/histidine 182, aspartic acid 48 and one or more of the following

1. Isoleucine 219 backbone amide nitrogen;
2. Glycine 218 backbone amide nitrogen;
3. Alanine 217 backbone amide nitrogen;
4. Serine 216 backbone amide nitrogen;
5. The side chain carboxylic acid group of aspartic acid 181;
6. The side chain guanidinium group of arginine 47;
7. Arginine 47 backbone amide nitrogen;

8. Aspartic acid 48 backbone amide nitrogen;
9. The side chain hydroxy group of tyrosine 46;
10. The side chain amino group of lysine 41;
11. The methylene side chain atoms of lysine 41;
12. The backbone amide carbonyl of asparagine 44;
13. The methylene side chain atoms of arginine 45;
14. The backbone amide carbonyl of arginine 45;
15. The methylene side chain atoms of arginine 47;
16. The methylene side chain atom of aspartic acid 48;
17. The backbone amide carbonyl of aspartic acid 48;
18. The methylene side chain atoms of leucine 88;
19. The side chain hydroxy group of serine 118;
20. The backbone amide carbonyl of leucine 119;
21. The side chain amide nitrogen of glutamine 262;
22. The side chain atoms of methionine 258;
23. The aromatic group of phenylalanine 52;
24. The backbone amide nitrogen of glycine 259;
25. The alpha-methylene atom of glycine 259;
26. The guanidinium group of arginine 254;
27. The methylene side chain atoms of arginine 254;
28. The methylene side chain atoms of arginine 24;
29. The guanidinium group of arginine 24; or
30. Any conserved water molecule in the vicinity of the active site.

Preferred key structural features of the inhibitors of the present invention include a phosphate isostere (**P**), a carboxylic acid perferably or a carboxylic acid or ortho-carboxylic acid or o-c acid isostere (**B**) and a hydrophobic group (**A**) as shown in Scheme 1.

Scheme 1.



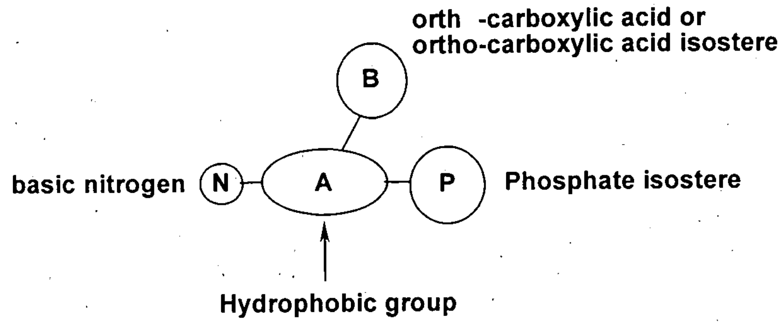
In a preferred embodiment, the key structural features of the inhibitors of the present invention include a phosphate isostere (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**) and a hydrophobic group (**A**), preferably a phenyl, naphthyl or thiophenyl as shown in Scheme 1.

In another preferred embodiment the key structural features of the inhibitors of the present invention include an oxalylamide (-NHCOCOOH) (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**) and a hydrophobic group (**A**).

In another preferred embodiment the key structural features of the inhibitors of the present invention include an oxalylamide (-NHCOCOOH) (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**) and a hydrophobic group (**A**), preferably a phenyl, naphthyl or thiophenyl as shown in Scheme 1.

In another preferred embodiment the key structural features of the inhibitors of the present invention include a phosphate isostere (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), a hydrophobic group (**A**) and a basic nitrogen (**N**) as shown in Scheme 2.

Scheme 2.

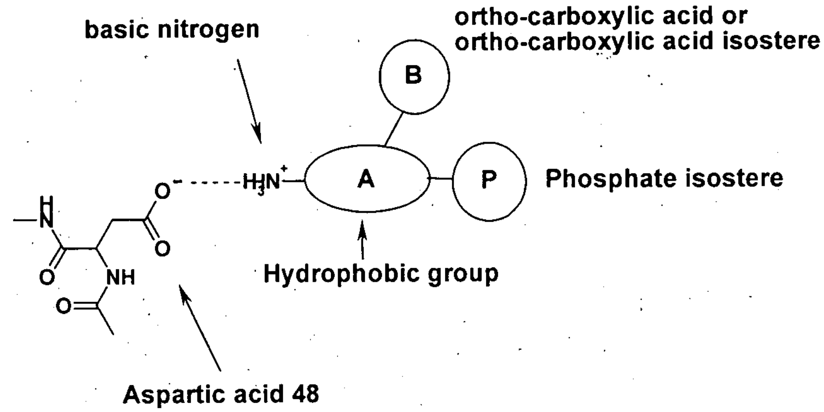


In another preferred embodiment, the key structural features of the inhibitors of the present invention include an oxalylamide (-NHCOCOOH) (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), a hydrophobic group (**A**) and a basic nitrogen (**N**) as shown in Scheme 2.

In another preferred embodiment, the key structural features of the inhibitors of the present invention include an oxalylamide (-NHCOCOOH) (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), a hydrophobic group (**A**), preferably a phenyl, naphthyl or thiophenyl and a basic nitrogen (**N**).

In another preferred embodiment, the key structural features of the inhibitors of the present invention include a basic nitrogen which provides selectivity for PTPases containing an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - a phosphate isostere (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), a hydrophobic group (**A**) as shown in Scheme 3.

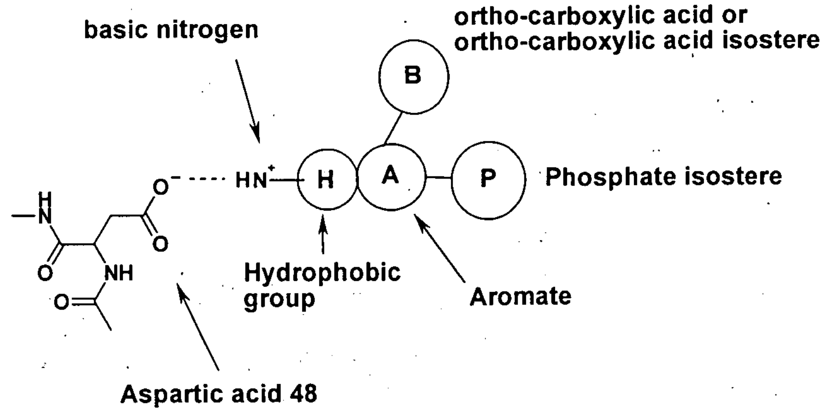
Scheme 3.



In another preferred embodiment, the key structural features of the inhibitors of the present invention include a basic nitrogen which provides selectivity for PTPases containing an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - an oxalylamide (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), a hydrophobic group (**A**) as shown in Scheme 3.

In another preferred embodiment, the key structural features of the inhibitors of the present invention include a basic nitrogen which provides selectivity for PTPases containing an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - an oxalylamide (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), and a hydrophobic group (**A**), preferably a phenyl, naphthyl or thiophenyl as shown in Scheme 3.

Scheme 4.



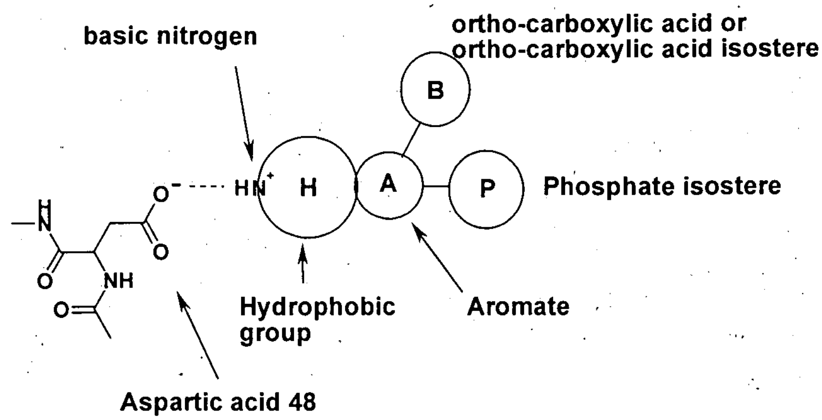
In another preferred embodiment, the key structural features of the inhibitors of the present invention include a basic nitrogen which provides selectivity for PTPases containing an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - a phosphate isostere (**P**), an ortho-carboxylic acid or ortho-carboxylic acid isostere (**B**), an aromatic group (**A**), preferably a phenyl or thiophenyl and a hydrophobic group (**H**) as shown in Scheme 4.

In another preferred embodiment, the key structural features of the inhibitors of the present invention include a basic nitrogen which provides selectivity for PTPases containing an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - an oxalylamide (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), an aromatic group (**A**), preferably a phenyl or thiophenyl and a hydrophobic group (**H**) as shown in Scheme 4.

In another preferred embodiment, the key structural features of the inhibitors of the present invention include a phosphate isostere (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), an aromatic group (**A**), preferably a phenyl or thiophenyl and a hydrophobic group (**H**) which include a basic nitrogen which provides selectivity for PTPases that

contain an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - as shown in Scheme 5.

Scheme 5.



In another preferred embodiment, the key structural features of the inhibitors of the present invention include an oxalylamide (**P**), an ortho-carboxylic acid or an ortho-carboxylic acid isostere (**B**), an aromatic group (**A**), preferably a phenyl or thiophenyl and a hydrophobic group (**H**) which include a basic which provides selectivity for PTPases that contain an aspartic acid in position 48 - via formation of a salt bridge to said aspartic acid 48 and repulsion to PTPases that contain the corresponding asparagine in position 48 - as shown in Scheme 5.

The key structural features of the inhibitors of the present invention described above are linked to each other via covalent bonds.

The compounds of the present invention possess, but are not limited to, a phosphate isostere in which the centroid of the phosphate isostere is 5.0-5.5 Å from the centroid of a carboxylic acid or carboxylic acid isostere, and 4.5-5.1 Å from the centroid of an aromatic group or a hydrophobic group. In a preferred embodiment, the compounds of the present invention possess, but are not limited to, an oxalylamide in which the centroid of the carboxylic acid moiety of said oxalylamide is 5.0-5.5 Å from the

centroid of a carboxylic acid or carboxylic acid isostere, and 4.5-5.1 Å from the centroid of an aromatic group or a hydrophobic group.

In an other preferred embodiment the compounds of the present invention possess, but are not limited to, a phosphate isostere in which the centroid of the phosphate isostere is 5.0-5.5 Å from the centroid of a carboxylic acid or carboxylic acid isostere, 4.5-5.1 Å from the centroid of an aromatic group or a hydrophobic group and 8.0-14.0 Å from a basic nitrogen. These features must participate in the appropriate interactions (e.g. hydrogen bonds, salt bridges, hydrophobic interactions, cation-π interactions, or π, π interactions, or aromatic-aromatic interactions) with the PTP1B and/or TC-PTP and/or other PTPases that are structurally similar to PTP1B active site and vicinity e.g. having an aspartic acid (Asp) in position 48. The centroid of the phosphate isostere should be 3.50-4.20 Å from the centroid of the side chain guanidinium group of arginine 221. The centroid of the carboxylic acid or carboxylic acid isostere should be 3.4-4.1 Å from the side chain amino group of lysine 120. The basic nitrogen should be 3.4-4.1 Å from the centroid of aspartic acid 48. The aromatic or, more generally, hydrophobic group should be near the following amino acid side chain atoms with appropriate distance ranges between the centroid of the side chain atoms and the centroid of the aromatic - or hydrophobic group given in parentheses: tyrosine 46 (4.4-5.1 Å) and phenylalanine/histidine 182 (4.4-6.5 Å).

The centroid of the oxalylamide carboxylic acid moiety should be 3.50-4.20 Å from the centroid of the side chain guanidinium group of arginine 221. The centroid of the carboxylic acid or carboxylic acid isostere should be 3.4-4.1 Å from the side chain amino group of lysine 120. The basic nitrogen should be 3.4-4.1 Å from the centroid of aspartic acid 48.

The aromatic - or hydrophobic group should be near the following amino acid side chain atoms with appropriate distance ranges between the centroid of the side chain atoms and the centroid of the aromatic - or hydrophobic group given in parentheses: tyrosine 46 (4.4-5.1 Å) and phenylalanine/histidine 182 (4.4-6.5 Å).

In a specific embodiment, the invention is directed to a method of inhibiting at least one intracellular or membrane-associated PTPase that has aspartic acid (Asp) in position 48 using the numbering for PTP1B, the method comprising exposing the PTPase to an inhibitor compound which fits spatially into the active site and the vicinity thereof, said compound comprising the following features and moieties:

I. (a) a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and a hydrogen bond with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; or (b) an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 wherein the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said

hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å;

and at least one of features IV through V:

IV. a hydrophobic group that interactswith the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

one or more of the following features VI-XXXVII:

VI. an amino group which forms a salt bridge to the site chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said site chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond or forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 is 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 is 2 ranges from.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that interacts with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that reaches a proximity interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid

of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of

said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and (i) the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, (ii) the centroid of said glycine 259 ranges from 4.7-7.7 Å, and (iii) the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

In another embodiment, the invention provides a method of inhibiting at least one PTPase selected from the group consisting of PTP1B, TC-PTP andother PTPase that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity therof , said compound comprising the following features and moieties:

I. (a) a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; or (b) an oxalylamide which forms a salt bridge to the guanidinium

group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or acid isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

one or more of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

one or more of the following featuresVI through XXXVII:

VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic

group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance

between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and

the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

In yet another embodiment, the invention provides a method of inhibiting a PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. (a) a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; or (b) an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

at lest one of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 3.55.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 is 4.4-6.5 Å; and one or more of the following features VI-XXXVII

VI. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å;

VII. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 is 3.4-4.1 Å;

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the

centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance

between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 is 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

Further provided is a method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B) and/or T-Cell Protein Tyrosine Phosphatase which (TC-PTP) and/or other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof , said compound comprising:

I. (a) a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a

hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; or (b) an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) acarboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å.

In another specific embodiment, the invention provides a method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B), T-Cell Protein Tyrosine Phosphatase (TC-PTP) and other PTPases that are structurally similar to PTP1B which comprises exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å;

wherein the distance between the centroid of the phosphate isostere and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said amino group ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said amino group ranges from 4.8-5.8 Å or

wherein the distance between the centroid of the phosphate isostere and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said oxygen atoms are ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said oxygen atoms are ranges from 5.0-7.9 Å.

The invention further provides a method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B), T-Cell Protein Tyrosine Phosphatase (TC-PTP) and other PTPases that are structurally similar to PTP1B which comprises exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

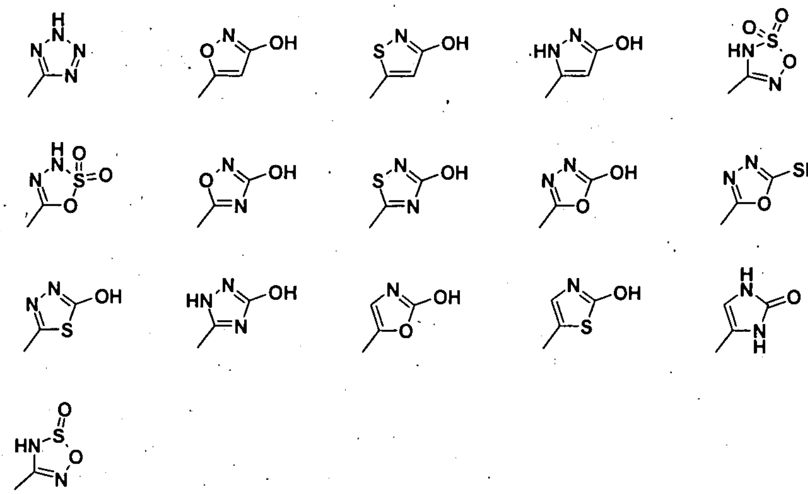
wherein the distance between the centroid of the carboxylic acid group of said oxalylamide group and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said amino group ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said amino group ranges from 4.8-5.8 Å or

wherein the distance between the centroid of the carboxylic acid group of said oxalylamide group and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said oxygen atoms are ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said oxygen atoms are ranges from 5.0-7.9 Å.

The hydrophobic groups that interact with tyrosine 46 and phenylalanine/histidine 182 include, but are not limited to, alkyl and aryl groups. These hydrophobic groups include cyclohexyl, phenyl, naphthyl, thiophenyl, pyrrolyl and furanyl. The hydrophobic groups that interact with one or more of the tyrosine 46 and the arginines 24, 45, 47, and 254 include, but are not limited to, alkyl and aryl groups. These hydrophobic groups include cyclohexyl, phenyl, naphthyl,thiophenyl, pyrrolyl and furanyl, optionally substitutedThe hydrophobic groups that interact with methionine 258, glycine 259 and phenylalanine 52 include, but are not limited to, alkyl and aryl groups groups. These aryl groups include phenyl, thiophenyl, pyrrolyl, furanyl, C_1-C_6alkyl and arylC_1-C_6alkyl which are defined hereinbelow.

The hydrophilic groups that interact with the hydrogen atom donated by the side chain amide nitrogen of arginine 47, aspartic acid 48, leucine 119, glycine 259, lysine 41, lysine 120, the side chain amide hydrogen atom donated by glutamine 262, the hydrogen atoms donated by the guanidinium group of arginine 254, arginine 45 or arginine 24 include, but are not limited to, hydroxy, C_1-C_6alkyloxy, aminocarbonyl, oxo, SO, SO_2,

$SONH_2$, SO_2NH_2, SO_2NHCF_3, COOH or a group selected from the following 5-membered heterocycles



The hydrophilic groups that interact with the side chain amide carbonyl group of asparagine 44, arginine 45 or aspartic acid 48 include, but are not limited to, amino, aminocarbonyl, hydroxy, $SONH_2$, SO_2NH_2, or SO_2NHCF_3.

The hydrophilic groups that interact with the side chain carboxylic acid group of aspartic acid 181 include, but are not limited to, amino, aminocarbonyl, hydroxy, C_1-C_6alkyloxy, $SONH_2$, SO_2NH_2.

The hydrophilic groups that interact with the side chain hydroxy group of serine 118 include, but are not limited to, aminocarbonyl, hydroxy, C_1-C_6alkyloxy, $SONH_2$, SO_2NH_2.

Unique structural elements in PTP1B

To identify unique residues or combinations of residues of PTP1B that could be utilised as points of interaction by selective inhibitors, alignment of the primary sequences of the catalytic domains of approximately 105 known vertebrate PTPases (Andersen,J.N. *et al.*, (1999) in preparation) was done (Table 1, below). Using the crystal structure of PTP1B (Andersen, H.S. *et al.* (1999) *J. Biol. Chem.* **275**:7107-7108 (2000);Barford, D., *et al. Science* **263:**1397-1404 (1994)), unique combinations of residues in the active site pocket or in its vicinity were

identified, i.e. in a distance (3-5.5 Å) that would allow simultaneous binding to the active site and these residues, while still retaining a low molecular weight (for example, below 700 dalton). In particular, the combination of 4 residues seems unique for the PTP1B family: arginine 47, aspartic acid 48, methionine 258, and glycine 259. arginine 47 and aspartic acid 48 contribute significantly to the binding of peptide substrates in PTP1B (Jia, Z.C., *et al.*, *Science* **268:**1754-1758 (1995)). A comparison of these regions in representative members of 14 PTP families, indicates that in particular residue 48 is an attractive binding element for selective PTP1B ligands since this residues is an aspartic acid in PTP1B and an asparagine in many other PTPases. Aspartic acid 48 is well-defined in the published PTP1B structures ((Puius, Y.A. *et al. Proc. Natl. Acad. Sci. USA* **94:**13420-13420 (1997)), (Pannifer, A.D.B., *et al.*, *J. Biol. Chem.* **273:**10454-10462 (1998)) and it is believed to play an important role in positioning substrates correctly relative to the active site (Sarmiento, M., *et al.*, *J. Biol. Chem.* **273:** 26368-26374 (1998)).

Table 1

Non-limiting examples of selected amino acid residues at positions in the vicinity of the active site (single letter code – PTP1B numbering)

Residue	PTP1B	SHP1	PTP-L1	PTPD2	PTPH1	STEP	IA-2	PTPβ	PTPα	PTPε	PTP-LAR	PTPμ	CD45	PTP
47	R	K	K	R	K	K	P	N	V	P	A	G	V	I
48	D	N	N	E	D	T	D	N	N	N	N	N	D	N
258	M	S	H	M	A	G	P	V	C	P	N	V	C	N
259	G	G	G	F	M	G	G	H	Q	Q	Y	N	L	Y

Optimization for potency

The key structural features of 2-(oxalyl-amino)-benzoic acid (OBA) are the twocarboxy groups respectively bound - directly and through a carbonylamino group - to an aromatic ring. Replacement of the phenyl ring

in OBA by thiophene, resulted in compounds with little difference in potency between the regioisomer 2-aminothiophene and 3-aminothiophene .

Previous studies have shown that phenyl-based phosphonate inhibitors have little affinity for PTP1B, while addition of a second phenyl ring (e.g. [(1,1-difluoro-1-naphthalenyl)-methyl]phosphonic acid) significantly increased the potency (Burke, T.R. *et al., Biochemistry* **35:**15989-15996 (1996)). The enhanced potency of the naphthalene ring system is due to extensive hydrophobic interactions with the side chains of tyrosine 46, valine 49, phenylalanine 182, alanine 217 and isoleucine 219. Similarly, 3-(oxalyl-amino)-naphthalene-2-carboxylic acid interacts with the same residues. It was reasoned that a saturated ring fused to 2-(oxalyl-amino)-thiophene-3-carboxylic acid (2-OTA) and/or 3-(oxalyl-amino)-thiophene-2-carboxylic acid (3-OTA) would serve a similar function and increase the potency. Further, the proposed binding mode of such a compound should bring the saturated ring in close proximity to residues arginine 47 and aspartic acid 48. Introducing a basic nitrogen or polar changes in this saturated ring would allow further interactions with the side chains or backbone amides of arginine 47 and aspartic acid 48. In accordance with the above alignment studies, we anticipated that selectivity for PTP1B and other PTPases with an aspartic acid in position 48 could be obtained by specifically addressing this area of the enzyme.

Consequently, 2-(oxalyl-amino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid (2-OBTA) was synthesised and its potency analysed against a set of PTPases. Table II shows that 2-OBTA is about 10-fold more potent against PTP1B than compounds 3-OTA and 2-OTA and 3-fold more potent than OBA when tested at pH 5.5 (the pH optimum for PTP1B using *p*NPP as substrate). Further, the inhibitory profile against this set of PTPases is almost the same as that of 3-(oxalyl-amino)-naphthalene-2-carboxylic acid. Thus, although 2-OBTA retains the features of a general PTP inhibitor, it already shows some selectivity for PTP1B. These results clearly indicate that 2-OBTA spatially fits in this region of PTP1B. Various substitutions in the saturated ring of 2-OBTA

were found to influence the binding affinities for different PTPases (not shown).

Table 2

K_i values (μM) – pH 5.5

	OBA	3-OTA	2-OTA	2-OBTA	2-OTPyA	2-OTPA
PTP1B	20	61	62	5.7	0.3	15
SHP-1	530	>2000	60	120	900	350
PTPα D1	700	500	1700	300	>2000	270
PTPε D1	125	350	590	45	600	20
PTPβ	32	160	18	14	150	12
CD45 D1D2	160	250	70	40	110	50
LAR D1D2	>2000	>2000	>2000	400	>2000	360

As indicated above, in comparison with OBA, 2-OBTA showed an approximately 3-fold increase in affinity for most PTPases. It was hypothesised that the saturated ring of 2-OBTA would occupy almost the same position as the distal ring of 3-(oxalyl-amino)-naphthalene-2-carboxylic acid, which was previously shown to bind in the proximity of arginine 47 and aspartic acid 48. Therefore, as expected, there was no apparent change in selectivity in accordance with the notion that the saturated ring makes hydrophobic contact with conserved residues such as tyrosine 46, alanine 217, valine/isoleucine219 and isoleucine/valine 49 (PTP1B numbering).

Optimization for selectivity

The combination of arginine 47 and aspartic acid 48 offers a rather unique, selective ligand-binding region in PTP1B. The side chains of both residues are charged at neutral pH and are therefore sutiable for salt bridge formation. Introducing a positive charge in 2-OBTA that could form a salt bridge with aspartic acid 48, would not only increase the potency of 20BTA against PTP1B but also – due to repulsive forces between the positive ligand charge and the asparagine side chain found in many other PTPases – decrease the affinity of 20BTA for these PTPases.

Three side chain rotamer conformations are normally defined for an aspartic acid residue (rota 1: 47.7%, rota 2: 33.6% and rota 3: 15.9%). In the published X-ray structures of PTP1B, two rotamers have been described, rota 1 and 3. The rota 3 conformation is stabilised by an internal hydrogen bond between the side chain and main chain amide with the side chain bending towards the active site pocket. Further, rota 3 seems to be the preferred rotamer for aspartic acid 48. The rota 1 conformation has only been found in four of the eleven published X-ray structures, and in three of these cases the rota 1 position is necessitated due to ligand occupancy. The aspartic acid 48 rota 1 conformation is pointing away from the active site pocket. Thus, rota 3 was found both in the apo-enzyme and in PTP1B complexed with peptide ligands that seem to stabilize this conformation. Further, we have recently co-crystallized PTP1B with OBA and 3 derivatives and found aspartic acid 48 in the rota 3 position in all structures (Andersen, H.S. *et al. J. Biol. Chem.* **275**, 7101-7108 (2000)). Based on these observations, it was hypothesized that introduction of a basic nitrogen in the saturated ring in 2-OBTA would be sufficiently close to aspartic acid 48 to allow the formation of a salt bridge. A recent survey of 322 unrelated proteins has shown that aspartic acid and asparagine residues have a strong tendency to form hydrogen bonds with neighboring backbone amides and in both cases with a significant preference for internal hydrogen bonds.

Assuming that asparagine 48 of other PTPases, e.g. PTPα, forms an internal hydrogen bond similar to that observed for aspartic acid 48 in PTP1B, the side chain amide of the asparagine with its positive dipole would be in an unfavourable position to the proposed basic nitrogen and thus cause repulsion.

2-(Oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid (2-OTPyA) - containing a positively charged tetrahydropyridine ring (pK_a > 10) - was synthesised in order to test the foregoing hypothesis. In agreement with the predictions, the affinity for PTP1B was increased about 20-fold without any significant increase in molecular weight (Table 2). Further, this compound showed an almost astonishing selectivity for

PTP1B *versus* all other PTPases tested. Again, this is in agreement with the hypothesis that repulsive forces between the basic nitrogen in 2-OTPyA and the positive dipole of the asparagine side chain decrease the potency against other PTPases. CD45, which also contains an aspartic acid in position 48, is a noticeable exception showing only a 2-fold decrease. It is speculated that the preferred rotamer of aspartic acid 48 in CD45 is the rota 1 conformation, which is too far away for salt bridge formation with 2-OTPyA. In addition, CD45 contains a valine in position 47, which may not have the same influence on aspartic acid 48 as an arginine.

2-(Oxalyl-amino)-4,7-dihydro-thieno[2,3-c]pyran-3-carboxylic acid (2-OTPA) - containing a negative dipole in the dihydropyran ring - was synthesised. In agreement with the predictions, the affinity for PTP1B was decreased about 2.5-fold compared to 2-OBTA without any significant increase in molecular weight (Table 2).

Table A (at the end of the specification) discloses the protein coordinates of PTP1B complexed with 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid (2-OTPA) and in Figure 1 is the active site of PTP1B complexed with 2-OTPA shown.

Optimization for potency towards Arginine 47 and Aspartic acid 48

Using further the combination of the 4 unique residues for the PTP1B family: arginine 47, aspartic acid 48, methionine 258, and glycine 259 it was hypothesised that an increase in potency could be obtained by introduction of a hydrogen-bond acceptor side chain that could form one or more hydrogen bonds with the main chain amides of arginine 47 and aspartic acid 48, would increase the potency against PTP1B.

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid (5-HTPyA) (Example 52) - still containing a positively charged tetrahydropyridine ring and three hydrogen-bond acceptors (oxygen atoms) - was synthesised. In

agreement with the predictions, the affinity for PTP1B was increased about 13- fold compared to 2-OTPyA.

Changing the positively charged nitrogen atom with a non charged oxygen atom and still addressing the main chain amides of arginine 47 and aspartic acid 48, it was hypothesised that an increase in general potency could be obtained. Thus, 5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (5-HTPA) (Example 4) - containing a non charged dihydropyran ring and three hydrogen-bond acceptor oxygen atoms - was synthesised. In agreement with the predictions, only the general potency was increased compared to 2-OTPyA as shown in Table 3.

Selectivity via steric hindrance

Referring again to the combination of the 4 residues unique for the PTP1B family: arginine 47, aspartic acid 48, methionine 258, and glycine 259, but this time more specifically to the combination of methionine 258 and glycine 259, which form part of a hydrophobic pocket in PTP1B in contrast to most other PTPases where the pocket is filled out: PTPα: cysteine 258-glutamine 259; PTP β: valine 258-histidine 259; PTP-LAR: asparagine 258-tyrosine 259; and CD45: cysteine 258-leucine 259 (PTP1B numbering), it was hypothesised that an increase in potency and selectivity could be obtained by introduction of a hydrophobic side chain that could form hydrophobic interactions to glycine 259 and to the side chain of methionine 258 and at the same time take part in repulsion-/steric hindrance with the same residues in other PTPases. Thus, 7-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (7-MOTPA) (Example 26) -- containing a hydrophobic 1,3-dihydro-isoindol side chain -- was synthesised. In agreement with the predictions, both affinity and selectivity for PTP1B was increased as shown in Table 3 compared to 2-OTPA.

Table 3

K_i values (μM) – pH 7

	2-OTPA	7-MOTPA	5-HTPA
PTP1B	63	1.2	1.9
PTPα D1	1100	620	93
PTPε D1	290	330	11
PTPβ	17	8.9	1.1
CD45 D1D2	960	380	130

Table B (at the end of the specification) discloses the protein coordinates of PTP1B complexed with 7-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (7-MOTPA) (Example 26), and Figure 2 shows the crystal structure of the active site of PTP1B complexed with 7-MOTPA.

Table C (at the end of the specification) discloses the protein coordinates of PTP1B complexed with 5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (5-HTPA) (Example 4), and Figure 3 shows the crystal structure of the active site of PTP1B complexed with 5-HTPA.

Table D (at the end of the specification) discloses the protein coordinates of PTP1B complexed with 2-(oxaly1-amino)-7-(1,1, 3-trioxo-1*H* -benzo [d] isothiazol-3-yloxomethyl)-4,7-dihydro-5*H,* thieno [2,3-c] pyran-3- carboxylic acid (example 54), including key water molecules. Figure 2 is the active site with selected water molecules shown.

Specific interactions of certain inhibitors of the present invention at the active site of PTP1B are detailed below.

The carboxy group of the oxamicN acid of 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid is positioned 2.9-3.0 Å from the guanidinium group of arginine 221 forming a salt bridge, as well as a hydrogen bond with the main chain amide of arginine 221 and serine 216, and the carbonyl forms a hydrogen bond with the main chain amide of glycine 220. The carboxy group in the 3 position is positioned 2.8 Å

from lysine 120 forming a salt bridge. The tetrahydro-thieno[2,3-c]pyridine ring forms hydrophobic interactions with phenylalanine 182, tyrosine 46, valine 49, alanine 217 and isoleucine 219. The basic nitrogen in the tetrahydro-thieno[2,3-c]pyridine ring is positioned 2.8 Å from the carboxy group of aspartic acid 48 forming a salt bridge.

The carboxy group of the oxamic acid of 7-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-thieno[2,3-c]pyran-3-carboxylic acid (Example 26) is positioned 2.9-3.0 Å from the guanidinium group of arginine 221 forming a salt bridge, as well as a hydrogen bond with the main chain amide of arginine 221 and serine 216, and the carbonyl forms a hydrogen bond with the main chain amide of glycine 220. The carboxy group in the 3 position is positioned 2.8 Å from lysine 120 forming a salt bridge. The dihydro-thieno[2,3-c]pyran ring forms hydrophobic interactions with phenylalanine 182, tyrosine 46, valine 49, alanine 217 and isoleucine 219. The phenyl ring of the isoindol ring forms a hydrophobic interaction with the side chain methylene atom of aspartic acid 48 and the 5-methoxy substituent forms hydrophobic interactions with the side chain atoms of methionine 258.

The carboxy group of the oxamic acid of 5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-thieno[2,3-c]pyran-3-carboxylic acid (Example 4) is positioned 2.9-3.0 Å from the guanidinium group of arginine 221 forming a salt bridge, as well as a hydrogen bond with the main chain amide of arginine 221 and serine 216, and the carbonyl forms a hydrogen bond with the main chain amide of glycine 220. The the carboxy group in the 3 position is positioned 2.7 Å from lysine 120 forming a salt bridge. The dihydro-thieno[2,3-c]pyran ring forms hydrophobic interactions with phenylalanine 182, tyrosine 46, valine 49, alanine 217 and isoleucine 219. The side chain methylene group at the 5 position of the thieno[2,3-c]pyran forms a hydrophobic interaction the side chain methylene group of aspartic acid 48. The phenyl ring of the isoindol ring forms a hydrophobic interaction with tyrosine 46 and both one of the oxo atoms and the hydroxy group at the isoindole forms hydrogen

bonds respectively with the main chain amide of aspartic acid 48 and arginine 47.

To further substantiate the generality in using steric hindrance/steric fit to obtain selectivity for PTP1B, TC-PTP and structurally similar PTPases we also synthesized 7-(1,1-dioxo-1H-benzo[d]isothiazol-3-yloxymethyl)-2-(oxalyl-amino)-4,7-dihyd ro-5H-thieno[2,3-c]pyran-3-carboxylic acid ("Compound N"). The substitution was introduced in the 7-position to address the region defined by residues 258 and 259. As indicated above, this part of PTP1B forms a hydrophobic pocket with direct access to the active site, whereas the same region is sterically hindered by more bulky side chains, in particular those corresponding to residue 259 in PTP1B. Compound N was synthesized with a substituent in the 7-position of 2-OTPA to sterically fit with this part of PTP1B and TC-PTP, but cause steric hindrance in other PTPs.

To test directly, whether the above compound was addressing the proposed region of PTP1B, Compound N was subjected to detailed enzyme kinetic analyses using a set of wildtype (wt) and mutant PTPs. Two enzymes, PTPα and PTPH1, were chosen as representatives for PTPs with bulky side chains in the 259 position. Using a combination of wt and PTP mutants it has previously been shown that Gln259 in PTPα, in addition to its direct effect, also indirectly influences the binding of inhibitors and substrates, most likely due to a negative influence on the rotational freedom of the side chain of Gln262 (Peters *et al.*, *J. Biol. Chem. 275*: 18201-18209 (2000)). As described above, selectivity can be obtained by introducing a basic nitrogen into 2-(oxalylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid that causes attraction in PTP1B due to salt bridge formation to Asp48 and repulsion against PTPs with an asparagine in the 48 position, such as PTPα. To analyze if the current approach based on steric hindrance is generally applicable, it was decided to include a PTP with an aspartic acid in position 48. PTPH1, which like PTP1B is an intracellular enzyme with one domain only, was

selected for these studies. The results of these studies are shown below (Table 4).

Table 4

Enzyme	Ki values (μM) at pH 7.0
PTP1B wt	0.4
PTP1B G259Q	65
PTP1B G259M	55
PTPα wt	>500
PTPα Q259G	70
PTPH1 wt	55
PTPH1 M259G	12

It appears that introduction of bulky side chains in the 259 position in PTP1B causes a very significant decrease in affinity for NNC 52-1153. Conversely, replacement of the bulky residues in PTPα and PTPH1 with a glycine increases the affinity. This clearly indicates that NNC 52-1153 addresses the 258-259 region of PTP1B.

Specificity against a broad set of PTPs –It was next analyzed if the side chain of NNC 52-1153 would cause the increased selectivity against other PTPs. NNC 52-1153 was tested against a set of 10 different wt PTP domains (Table 5). It appears from this table that a substantial increase in affinity for PTP1B and TC-PTP has been obtained, while at the same time introducing a very high degree of selectivity against many other PTPs representing a broad spectrum of this class of enzymes (having Asp 48).

Table 5

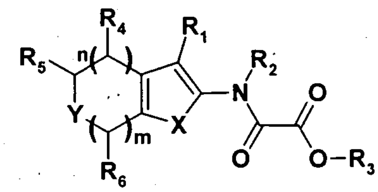
Enzyme	Ki values (μM) at pH 7.0
PTP1B	0.4
TC-PTP	0.6
PTPH1	55
PTPα	700
PTPε	460
CD45	500

LAR	120
GLEPP1	150
PTPβ	15

To unequivocally determine the binding mode, x-ray co-crystallization studies of PTP1B and NNC 52-1153 were initiated. A well-suited electron density was identified in the active site pocket. The oxalylamino and o-carboxy groups show the exact same interaction with the PTP signature motif and salt bridge formation to Lys120 as described previously for 2-(oxalylamino)-benzoic acid and the thiophene-based derivatives. Significantly, the side chain of the ligand is positioned in close vicinity to residues 258 and 259. Several interaction points appear to be responsible for the observed significant increase in affinity for PTP1B. Thus, a long hydrogen bond seems to interact with one carbonyl of the ligand side chain. In addition, important van der Waals contacts are made between the aromatic ring of the ligand side chain and the side chain of Met248 and Cβ atom of Asp48.

As described above, we have utilized salt bridge formation to Asp48 to obtain potent and selective PTP1B inhibitors. In these structures, Asp48 was in the so-called rotamer ("rota") 3 position – pointing towards the active site. In contrast, the side chain of Asp48 is pushed away from the active site by the oxygen molecules in NNC 52-1153 (i.e. the rotamer 1 position). This allows a novel water molecule to form a bridge between the two oxygen molecules in the ligand and Asp48. This surprising observation can be used to design additional inhibitors of PTP1B.

The present invention encompasses, but is not limited to, compounds of the Formula 1 wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined below;



Formula 1

In the above Formula 1

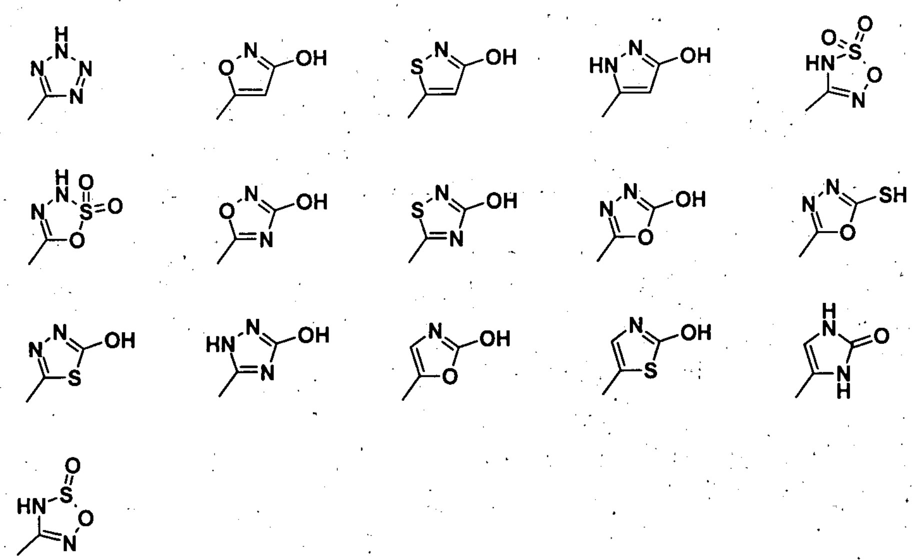
n is 0, 1 or 2 (if m = 0 then n is 1 or 2);

m is 0, 1 or 2 (if n = 0 then m is 1 or 2);

X is S, O, NR_8;

Y is NR_7, O, S, SO, SO_2;

R_1 is hydrogen, $COOR_3$, or selected from the following 5-membered heterocycles:



R_2 is hydrogen, C_1-C_6alkyl, hydroxy, NR_9R_{10};

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-

carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, aryloxy C_1-C_6 alkyl, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_9R_{10}, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{13}, arylC_1-C_6alkylcarbonyl-amino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, arylamino carbonylaminoC_1-C_6 alkyl, arylaminoC_1-C_6 alkyl, arylcarbonylamino C_1-C_6 alkyl, $CONR_9R_{10}$, $R_8R_9NC_1$-C_6 alkyl,or C_1-C_6alkyl-$CONR_9R_{10}$ wherein the alkyl and aryl groups are optionally substituted and R_{13} is NR_9R_{10}, or C_1-C_6alkylNR_9R_{10};

R_7 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, R_9R_{10}NcarbonylC_1-C_6alkyl wherein R_9 and R_0 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted;

R_8 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkyl-carboxy wherein the alkyl and aryl groups are optionally substituted;

R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or

R_9 and R_{10} are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or

tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, $NR_{11}R_{12}$ or C_1-C_6alkylamino-C_1-C_6alkyl, wherein R_{11} and R_{12} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_9 and R_{10} are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

The compounds of Formula 1 are oxalylamide compounds having in common key structural features required of non hydrolysable protein tyrosine phosphatase inhibitors, most particularly PTP1B and/or TC-PTP inhibitors. These structural features endow the present compounds with the appropriate molecular shape necessary to fit into the enzymatic active site, to bind to such site in a non covalently way, thereby blocking the site and inhibiting enzymatic biological activity. Referring to Formula 1, such structural features include the oxalylamide and an ortho-carboxylic acid attached to a hydrophobic group, preferably an aryl as defined below
The compounds of the invention can be further modified to act as pro-drugs.
It is a well known problem in drug discovery that compounds, such as enzyme inhibitors, may be very potent and selective in biochemical assays, yet be inactive in vivo. This lack of so-called bioavailability may be ascribed to a number of different factors such as lack of or poor absorption in the gut, first pass metabolism in the liver, poor uptake in cells. Although the factors determining bioavailability are not completely understood, there are many examples in the scientific literature - well-known to those skilled in the art - of how to modify compounds, which are potent and selective in biochemical assays but show low or no activity in

vivo, into drugs that are biologically active. It is within the scope of the invention to modify the compounds of the invention, termed the 'original compound' or "prototype", by attaching chemical groups that will improve the bioavailability of said compounds in such a way that the uptake in cells or mammals is facilitated. Examples of said modifications, which are not intended in any way to limit the scope of the invention, include changing of one or more carboxy groups to esters (for instance methyl esters, ethyl esters, acetoxymethyl esters or other acyloxymethyl esters). Compounds of the invention, original compounds, modified by attaching chemical groups are termed 'modified compounds' Said chemical groups may or may not be apparent in the claims of this invention. Other examples of modified compounds, which are not intended in any way to limit the scope of the invention, are compounds that have been cyclized at specific positions - so called 'cyclic compounds' - which upon uptake in cells or mammals become hydrolyzed at the same specific position(s) in the molecule to yield the compounds of the invention, the original compounds, which are then said to be 'non-cyclic'For the avoidance of doubt, it is understood that the latter original compounds in most cases will contain other cyclic or heterocyclic structures that will not be hydrolyzed after uptake in cells or mammals. Generally, said modified compounds will not show a behavior in biochemical assays similar to that of the original compound, i.e. the corresponding compounds of the invention without the attached chemical groups or said modifications. Said modified compounds may even be inactive in biochemical assays. However, after uptake in cells or mammals these attached chemical groups of the modified compounds may in turn be removed spontaneously or by endogenous enzymes or enzyme systems to yield compounds of the invention, original compounds. 'Uptake' is defined as any process that will lead to a substantial concentration of the compound inside cells or in mammals. After uptake in cells or mammals and after removal of said attached chemical group or hydrolysis of said cyclic compound, the compounds may have the same structure as the original compounds and thereby regain their activity and hence become active in cells and/or in vivo after uptake. A number of procedures, well known to those skilled in the art,

may be used to verify that the attached chemical groups have been removed or that the cyclic compound has been hydrolyzed after uptake in cells or mammals. An example, which is not intended in any way to limit the scope of the invention, is given in the following. A mammalian cell line, which can be obtained from the American Tissue Type Collection or other similar governmental or commercial sources, is incubated with said modified compound. After incubation at conditions well known to those skilled in the art, the cells are washed appropriately, lysed and the lysate is isolated. Appropriate controls, well known to those skilled in the art, must be included. A number of different procedures, well known to those skilled in the art, may in turn be used to extract and purify said compound from said lysate. Said compound may or may not retain the attached chemical group or said cyclic compound may or may not have been hydrolyzed. Similarly, a number of different procedures - well known to those skilled in the art - may be used to characterize said purified compound structurally and chemically. Since said purified compound has been isolated from said cell lysate and hence has been taken up by said cell line, a comparison of said structurally and chemically characterized compound with that of the original unmodified compound (i.e. without said attached chemical group or said non-cyclic compound) will immediately provide to those skilled in the art information on whether the attached chemical group as been removed in the cell or whether the cyclic compound has been hydrolyzed. As a further analysis, said purified compound may be subjected to enzyme kinetic analysis as described in detail in the present invention. If the kinetic profile is similar to that of the original compound without said attached chemical group, but different from said modified compound, this confirms that said chemical group has been removed or said cyclic compounds has been hydrolyzed. Similar techniques may be used to analyze compounds of the invention in whole animals and mammals.

Preferred prodrug classes for the present compounds include acyloxymethyl esters or acyloxymethyl carbamates of the compounds of the present invention which may be prepared by the following general

procedure *(C.Schultz et al, J. Biol. Chem.,* **1993**, *268,* 6316-6322.*)* and (Alexander, J. *et al*, *J. Med. Chem.* **1991**, *34*, 78-81).

A carboxylic acid (1 equivalent) is suspended in dry acetonitrile (2 ml per 0.1 mmol). Diisopropyl amine (3.0 equivalents) is added followed by bromomethyl acetate (1.5 equivalents). The mixture is stirred under nitrogen overnight at room temperature. Acetonitrile is removed under reduced pressure to yield an oil which is diluted in ethyl acetate and washed with water (3 x). The organic layer is dried over anhydrous magnesium sulfate. Filtration followed by solvent removal under reduced pressure affords a crude oil. The product is purified by column chromatography on silica gel, using an appropriate solvent system.

DEFINITIONS

As used herein, the term "attached" or "-" (e.g. $-C(O)-R_{13}$, which indicates the carbonyl attachment point to the scaffold) signifies a stable covalent bond, certain preferred points of attachment points being apparent to those skilled in the art.

The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes C_1-C_6 straight chain saturated, methylene and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_1-C_6 branched saturated and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_3-C_6 cyclic saturated and C_5-C_6 unsaturated aliphatic hydrocarbon groups, and C_1-C_6 straight chain or branched saturated and C_2-C_6 straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_6 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, ethenyl, propenyl, butenyl, penentyl, hexenyl,

isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, and the like. The alkyl group as defined above is optionally substituted wherein the substitutents are independently selected from halo, cyano, nitro, trihalomethyl, carbamoyl, hydroxy, oxo, $COOR_3$, $CONR_9R_{10}$, C_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, thio, C_1-C_6alkylthio, arylthio, arylC_1-C_6alkylthio, NR_9R_{10}, C_1-C_6alkylamino, arylamino, arylC_1-C_6alkylamino, di(arylC_1-C_6alkyl)amino, C_1-C_6alkylcarbonyl, arylC_1-C_6alkyl-carbonyl, C_1-C_6alkylcarboxy, arylcarboxy, arylC_1-C_6alkylcarboxy, C_1-C_6alkylcarbonylamino, -C_1-C_6alkylaminoCOR_{14}, arylC_1-C_6alkylcarbonyl-amino, tetrahydrofuranyl, morpholinyl, piperazinyl, -$CONR_9R_{10}$, -C_1-C_6-alkyl$CONR_9R_{10}$, or a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam; wherein R_{14} is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy and R_3 is defined as above or NR_9R_{10}, wherein R_9, R_{10} are defined as above.

The term “saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system” represents but are not limit to aziridinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, indolyl, isoindolyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinoxalinyl, indolinyl, indazolyl, benzimidazolyl, benzotriazolyl, purinyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, iminodibenzyl, iminostilbenyl.

The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an “alkyl” group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "alkyloxyalkyl" represents an “alkyloxy” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term “alkyloxyalkyloxy” represents an "alkyloxyalkyl" group attached through an oxygen atom as defined above having the indicated number of carbon atoms.

The term "aryloxy" (e.g. phenoxy, naphthyloxy and the like) represents an aryl group as defined below attached through an oxygen bridge.
The term "arylalkyloxy" (e.g. phenethyloxy, naphthylmethyloxy and the like) represents an “arylalkyl” group as defined below attached through an oxygen bridge.

The term "arylalkyloxyalkyl" represents an “arylalkyloxy” group as defined above attached through an “alkyl” group defined above having the indicated number of carbon atoms.

The term "arylthio" (e.g. phenylthio, naphthylthio and the like) represents an “aryl” group as defined below attached through an sulfur bridge.

The term “alkyloxycarbonyl” (e.g. methylformiat, ethylformiat and the like) represents an “alkyloxy” group as defined above attached through a carbonyl group.

The term “aryloxycarbonyl” (e.g. phenylformiat, 2-thiazolylformiat and the like) represents an “aryloxy” group as defined above attached through a carbonyl group.
The term “arylalkyloxycarbonyl” (e.g. benzylformiat, phenyletylformiat and the like) represents an “arylalkyloxy” group as defined above attached through a carbonyl group.
The term “alkyloxycarbonylalkyl” represents an “alkyloxycarbonyl” group as defined above attached through an “alkyl” group as defined above having the indicated number of carbon atoms.
The term “arylalkyloxycarbonylalkyl” represents an “arylalkyloxycarbonyl” group as defined above attached through an “alkyl” group as defined above having the indicated number of carbon atoms.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the like) represents an “alkyl” group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "arylalkylthio" (e.g. phenylmethylthio, phenylethylthio, and the like) represents an “arylalkyl” group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "alkylthioalkyl" represents an “alkylthio” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylthioalkyl" represents an “arylalkylthio” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-hexylamino, (2-cyclopentyl)propylamino, hexenylamino, pyrrolidinyl, piperidinyl and the like) represents one or two “alkyl” groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10}, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_9 and R_{10} are defined as above.

The term "arylalkylamino" (e.g. benzylamino, diphenylethylamino and the like) represents one or two “arylalkyl” groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two “arylalkyl” groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl,

arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10}, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_9 and R_{10} are defined as above.

The term "alkylaminoalkyl" represents an “alkylamino” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylaminoalkyl" represents an “arylalkylamino” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term “arylalkyl” (e.g. benzyl, phenylethyl) represents an “aryl” group as defined below attached through an alkyl having the indicated number of carbon atoms or substituted alkyl group as defined above.

The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl) represents an “alkyl” group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term “arylcarbonyl” (benzoyl) represents an “aryl” group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. phenylcyclopropylcarbonyl, phenylethylcarbonyl and the like) represents an “arylalkyl” group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "alkylcarbonylalkyl" represents an “alkylcarbonyl” group attached through an “alkyl” group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarbonylalkyl" represents an “arylalkylcarbonyl” group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an “alkylcarbonyl” group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term “arylcarboxyalkyl” (e.g. phenylcarboxymethyl) represents an

"arylcarbonyl" group defined above wherein the carbonyl is in turn attached through an oxygen bridge to an alkyl chain having the indicated number of carbon atoms.

The term "arylalkylcarboxy" (e.g. benzylcarboxy, phenylcyclopropylcarboxy and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term "alkylcarboxyalkyl" represents an "alkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarboxyalkyl" represents an "arylalkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylamino" (e.g. benzylcarbonylamino and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkyl" represents an "alkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylaminoalkyl" represents an "arylalkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkylcarbonyl" represents an alkylcarbonylaminoalkyl group attached through a carbonyl group. The nitrogen atom may be further substituted with an "alkyl" or "aryl" group.

The term "aryl" represents a substituted or unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalo-methyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, $COOR_3$, $CONR_9R_{10}$, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_9R_{10}, C_1-C_6-alkylamino, C_1-C_6alkylaminoC_1-C_6alkyl, arylamino, arylC_1-C_6alkylamino, arylC_1-C_6alkyl-aminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyl-carbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxy-C_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, carboxyC_1-C_6alkyl-oxy, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{14}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -$CONR_9R_{10}$, or -C_1-C_6alkyl$CONR_9R_{10}$; wherein R_3, R_9, R_{10}, and R_{14} are defined as above and the alkyl and aryl groups contained therein are optionally substituted as defined above. The definition of aryl includes but is not limited to phenyl, biphenyl, indenyl, fluorenyl, naphthyl (1-naphthyl, 2-naphthyl), pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiophenyl (2-thiophenyl, 3-thiophenyl, 4-thiophenyl, 5-thiophenyl), furanyl (2-furanyl, 3-furanyl, 4-furanyl, 5-furanyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl), 5-tetrazolyl, pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-

isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo-[b]furanyl), 6-(2,3-dihydro-benzo-[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]-thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]-thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]-thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]-thiophenyl)), 4,5,6,7-tetrahydro-benzo[b]thiophenyl (2-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 3-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 4-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 5-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 6-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 7-(4,5,6,7-tetrahydro-benzo[b]thiophenyl)), 4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl (4-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 5-4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 6-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 7-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl)), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl (1-isoindolyl, 2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), 1,3-dihydro-isoindolyl (1-(1,3-dihydro-isoindolyl), 2-(1,3-dihydro-isoindolyl), 3-(1,3-dihydro-isoindolyl), 4-(1,3-dihydro-isoindolyl), 5-(1,3-dihydro-isoindolyl), 6-(1,3-dihydro-isoindolyl), 7-(1,3-dihydro-isoindolyl)), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benz-oxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzo-thiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz-[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz-[b,f]azepine-4-yl, 5H-dibenz[b,f]-azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-

dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz-[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), pyrrolidinyl (1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), phenylpyridyl (2-phenyl-pyridyl, 3-phenyl-pyridyl, 4-phenylpyridyl), phenylpyrimidinyl (2-phenylpyrimidinyl, 4-phenyl-pyrimidinyl, 5-phenylpyrimidinyl, 6-phenylpyrimidinyl), phenylpyrazinyl, phenylpyridazinyl (3-phenylpyridazinyl, 4-phenylpyridazinyl, 5-phenyl-pyridazinyl).

The term "arylcarbonyl" (e.g. 2-thiophenylcarbonyl, 3-methoxy-anthrylcarbonyl, oxazolylcarbonyl) represents an "aryl" group as defined above attached through a carbonyl group.
The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)propylcarbonyl, (2-chloronaphthyl)pentenylcarbonyl, imidazolylcyclopentylcarbonyl) represents an "arylalkyl" group as defined above wherein the "alkyl" group is in turn attached through a carbonyl.
The term "aryloxyalkyl" represents an "aryloxy" group as defined above attached through an "alkyl" group defined above having the indicated number of carbon atoms.

The term "arylaminocarbonylaminoalkyl" represents an "arylaminocarbonylamino" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "R8R9Nalkyl" is as defined under "substituted alkyl" or "optionally substituted alkyl".

The term "arylaminoalkyl" represents an "arylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylcarbonylaminoalkyl" represents an "arylcarbonylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

As used herein, the term "vicinity" applied with respect to the active site of a PTPase means the space occupied by a half sphere – with its apex pointing towards aspartic acid 48 - having its center in the side chain nitrogen atom of the guanidinium group of residue 221 (arginine), which points away from the phosphate binding loop (residue Arg221 to Cys215). The radius of the half sphere is 27 Å.

As used herein, the term "structurally similar" means any PTPase that contains an aspartic acid in residue position 48 (PTP1B numbering – as defined in Chernoff et al, 1989, *supra*) and is more than 50 % identical and preferably more than 65 % identical and most preferably more than 80 % identical to PTP1B (Chernoff et al., *supra*) and/or TC-PTP (Cool et al., Proc. Natl. Acad. Sci. U.S.A. 86: 5257-5261 (1989)) at the primary amino acid sequence level in the catalytic domain as defined below. Percent indentity can be determined using standard algorithms e.g. BLAST, BLASTP MEGALIGN, etc using default parameters.

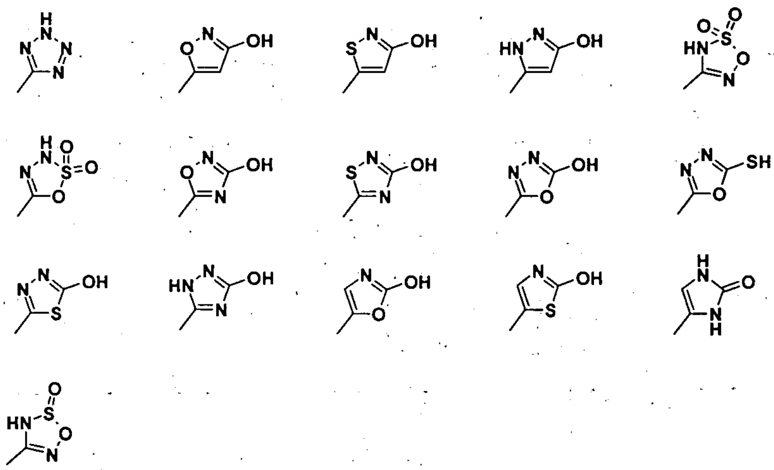
As used herein, the term "catalytic domain" means the primary amino acid sequence of a PTPase that corresponds to the primary amino acid sequence between Asn 40 and Gln 262 (both residues included) in PTP1B (Chernoff et al., *supra*).

As used herein, the term "centroid" means the position for the stated atoms calculated by averaging the x coordinates of the atoms to obtain the x coordinate of the centroid, averaging the y coordinates of the atoms to obtain the y coordinate of the centroid, and averaging the z coordinates of the atoms to obtain the z coordinate of the centroid.

As used herein, the term "phosphate isostere" means a chemical group, which binds to one or more of the side chains or the main chain of the residues in the so-called P-loop or PTP signature motif of PTPases (i.e. Cys215-Xxx216-Xxx217-Xxx218-Xxx219-Xxx220-Arg221, where Cys215 and Arg221 are absolutely conserved, whereas Xxx stands for less conserved residues). In PTP1B the P-loop residues are: Cys215-

Ser216-Ala217-Gly218-Ile219-Gly220-Arg221). As a non limiting example the following groups are phosphate isosteres: $-CH_2PO(OH)_2$, $-CHFPO(OH)_2$, $-CF_2PO(OH)_2$, -NHCOCOOH, $-OCH(COOH)_2$, $-OCF(COOH)_2$, $-OCH_2COOH$. $-CONHCH_2COOH$, -CONHCHFCOOH and $-CONHCF_2COOH$.

As used herein, the term "carboxylic acid isostere" means a compound resembling a carboxy group in its electronic and steric configuration and in its biological action (effecting inhibition of the class of structurally similar PTPases) but having a different chemical structure. As a non limiting example, the following residues and heterocycles are carboxylic acid isosteres: $-CONH_2$, $-SONH_2$, $-SO_2NH_2$,



As used herein the term "interact" or "interaction" when used in the context of a moiety or group of an inhibitor interacting with the active site or vicinity thereof of a PTPase, means the formation of noncovalent bonds, such as hydrogen bonds, salt bridges, hydrophobic interactions van der Waals forces, cation π interactions, or π, π interactions, aromatic-aromatic interactions, (Copeland, Enzymes-a practical introduction to structure, mechanism, and data analysis, VCH Publishers, Inc..New York (1996)) or by forming covalent bonds. Preferably, interactions between inhibitors of the invention and PTPs occur through non-covalent bonds.

As used herein, the term "hydrophobic" means a nonpolar chemical group (e.g. phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclohexyl, *tert*-butyl, isopropyl as nonlimiting examples) when present in the aqueous

phase, in the vicinity of an enzyme, its hydrocarbon framework disturbs the degree of randomness of the water molecules, which forces the water molecules to associate by hydrogen bonding to form quasi-crystalline clusters or "ice-bergs". This localized increase in the ordered structure of water will result in a loss of entropy, accompanied by an increase in the free energy of the system. Thus, a driving force operates to reject the hydrocarbon region of the drug/inhibitor from the aqueous phase so that binding to one or more similar hydrocarbon chain(s) within the enzyme molecule is facilitated.

As used herein, the term "hydrogen bond" means an association between an electronegative atom, e.g. fluorine, oxygen, nitrogen, or sulfur, and a hydrogen atom attached to another such electronegative atom.

As used herein, the term "salt bridge" means any electrostatic bond between positively and negatively charged groups.

The compounds of the present invention have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

Pharmaceutically acceptable salts of the compounds of formula 1, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as -COOH, 5-tetrazolyl or $-P(O)(OH)_2$, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethane sulfonate, picrate and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, can be used as the dosage form.

Also, in the case of the -COOH or -P(O)(OH)$_2$ being present, pharmaceutically acceptable esters can be employed, e.g., methyl, *tert*-butyl, acetoxymethyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

As used herein, “treatment” shall include therapeutic or preventative management, treatment, cure, or palliation of a disease state or a measurable delay in its onset or recurrence or measurable reduction in its severity.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other other biological or clinical investigator.Also included in the present invention is a process for isolation of PTPases via affinity purification procedures based on the use of immobilized compounds of the invention. Isolation can be effected using procedures otherwise well-known to those skilled in the art. Such methods, may be used to identify novel PTPases or other molecules with phosphotyrosine recognition units and to elucidate the function of both novel and previously identified PTPases. As a non-limiting example, compounds of the invention may be immobilized by coupling to a solid-phase support, such as as exemplified in examples 119 and 120. See also Example 121. A tissue sample or a sample from a cell line prepared as a lysate by methods well-known to those skilled in the art may be passed over said solid-phase coupled with a compound of the invention. After appropriate washing procedures designed to remove material that binds nonspecifically to said solid-phase, using standard procedures well known to those skilled in the art, mostly PTPases or other molecules with phosphotyrosine recognition units will be bound to the compounds of the invention coupled to the

solid phase. Said PTPases or other molecules with phosphotyrosine recognition units may in turn be released by procedures well-known in the art and further subjected to amino acid sequence analysis according to standard procedures well-known to those skilled in the art. By back-translation of said amino acid sequence into a nucleotide sequence of the corresponding cDNA can be deduced using the appropriate genetic code. Said nucleotide sequence can be used to design and produce an equivalent oligonucleotide, which in turn can be used to identify partial or full-length cDNA clones from appropriate cDNA libraries encoding a protein or glycoprotein corresponding to or similar to the isolated PTPase or molecule with pTyr recognition units. Said oligonucleotide or isolated cDNA clone(s) can similarly be used to isolate genomic clones corresponding to said cDNA clones. Said partial or full-length cDNA can be inserted into appropriate vectors and expressed and purified proteins with procedures well known to those skilled in the art. Said purified proteins, in particular PTPases, may be used to further analyze the inhibitory capacity and selectivity of compounds of the invention as described.

The invention is further directed to compounds of the invention coupled to a suitable solid-phase matrix such as a Wang-resin or a Rink-resin, e.g., for further synthesis, combinational synthesis, or as a support for affinity purification.

The invention is further directed to a method for isolating a protein or a glycoprotein with affinity for a compound according to the invention from a biological sample, comprising:

- contacting a compound of the invention immobilized by coupling to a suitable solid-phase matrix with said biological sample in order for said immobilized compound to form a complex by binding said protein or glycoprotein,
- removing unbound material from said biological sample and isolating said complex, and
- extracting said protein or glycoprotein from said complex.

The invention is further directed to a method for isolating a protein-tyrosine phosphatase with affinity for a compound according to the invention from a biological sample, comprising

- contacting a compound of the invention immobilized by coupling to a suitable solid-phase matrix with said biological sample in order for said immobilized compound to form a complex by binding said protein-tyrosine phosphatase
- removing unbound material from said biological sample and isolating said complex
- extracting said protein-tyrosine phosphatase.

The following compounds are encompassed by the invention:
5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalylamino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester methyl ester;
Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester;
7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester;

7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)-carbamoyl)-nicotinic acid;

5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Amino-3-phenyl-propionylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

(L)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((Benzo[1,3]dioxole-5-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-(4-Methanesulfonyl-phenyl)acetylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(S)-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(R)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(S)-(Oxalyl-amino)-5-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-((4-Acetylamino-benzylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(S)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(S)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(R)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(R)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(R),7-(R)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid; or a pharmaceutically acceptable salt thereof

PHARMACOLOGICAL METHODS

The compounds are evaluated for biological activity with a truncated form of PTP1B (corresponding to the first 321 amino acids), which was expressed in E. coli and purified to apparent homogeneity using published procedures well-known to those skilled in the art. The enzyme reactions are carried out using standard conditions essentially as described by Burke *et al.* (*Biochemistry* **35**; 15989-15996 (1996)) incorporated by reference. The assay conditions are as follows. Appropriate concentrations of the compounds of the invention (e.g.,0.1 to 100μM) are added to the reaction mixtures containing different concentrations of the substrate, *p*-nitrophenyl phosphate (range: 0.16 to 10 mM - final assay concentration). The buffer used was 50 mM HEPES pH 7.0, 100 mM sodium chloride, 0.1 % (w/v) bovine serum albumin, 5 mM glutathione, and 1 mM EDTA. The reaction was started by addition of the enzyme and carried out in microtiter plates at 25° C for 60 minutes. The reactions are stopped by addition of NaOH. The enzyme activity was determined by measurement of the absorbance at 405 nm with appropriate corrections for absorbance at 405 nm of the compounds and *p*-nitrophenyl phosphate. The data are analyzed using nonlinear regression fit to classical Michaelis Menten enzyme kinetic models. Inhibition is expressed as K_i values in μM. The results of representative experiments are shown in Table 6.

Tabl 6.

Inhibition of classical PTPases by compounds

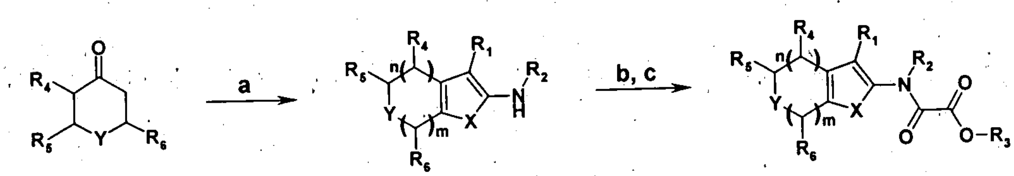
of the invention

	K_I (μM) at pH 7				
	PTP1B	TC-PTP	PTP α	PTP β	PTP ε
	residue 48 Asp	residue 48 Asp	residue 48 Asn	residue 48 Asn	residue 48 Asn
Example No.					
48	0.25		900	47	380
49	0.085			8.6	
50	0.07		1000	8	
52	1.2		> 400	107	> 500

THE SYNTHESIS OF THE COMPOUNDS

In accordance with one aspect of the invention, compounds of the invention are prepared as illustrated in the following reaction schemes wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined as above:

Method A



a) $NCCH_2COOR_3$, sulphur, morpholine or triethylamine, ethanol; b) R_3OCOCOimidazole, tetrahydrofuran; c) 25 % trifluoroacetic acid/dichloromethane.

Method B

The pharmaceutical carrier employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatine, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil, water, and physiologic saline.

Similarly, the carrier or diluent may include any material that impacts controlled release of taste-masking properties, known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Generally, the compounds of this invention are dispensed in unit dosage form comprising 10-200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-500 mg/day, e.g. about 100 mg per dose, when administered to patients, e.g. humans, as a drug.

A typical tablet that may be prepared by conventional tabletting techniques contains

<u>Core:</u>

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Areosil®)	1.5 mg
Cellulose, microcryst. (Avicel®)	70 mg

Modified cellulose gum (Ac-Di-Sol®)	7.5 mg
Magnesium stearate	

Coating:

HPMC	approx.	9 mg
*Mywacett® 9-40 T	approx.	0.9 mg

*Acylated monoglyceride used as plasticiser for film coating.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intranasal, intramuscular, topical, intravenous, intraurethral, ophthalmic solution or an ointment, the oral route being preferred.

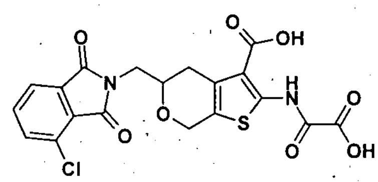
EXAMPLES

The process for preparing compounds of Formula 1 and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

Hereinafter, TLC is thin layer chromatography, $CDCl_3$ is deuterio chloroform, CD_3OD is tetradeuterio methanol and DMSO-d_6 is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^{1}H NMR shifts (δ_H) are given in parts per million (ppm) down field from tetramethylsilane as internal reference standard. M.p.: is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still *et al.*, *J. Org. Chem. 43:* 2923 (1978) on Merck silica gel 60 (Art. 9385). HPLC analyses are performed using 5μm C18 4 x 250 mm column eluted with various mixtures of water and acetonitrile, flow = 1 ml/min, as described in the experimental section.

Wang-resin is polystyrene with a 4-hydroxymethylphenol ether linker. Compounds used as starting material are either known compounds or compounds which can readily be prepared by methods known per se.

EXAMPLE 1



5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of benzyloxyacetaldehyde (8.3 g, 0.06 mol) in benzene (80 mL) was added 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (10.6 g, 0.06 mol). The reaction mixture was stirred under nitrogen for 15 min., cooled to 0 °C and a solution of 0.5 M zinc chloride (55 ml, 0.03 mol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and evaporated in vacuo. The resultant oil was diluted with ethyl acetate (100 ml), washed with 1N hydrochloric acid (3 x 50ml), saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$) and evaporated in vacuo. The resulting oil was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (1:2) as eluant. Pure fractions were collected affording after evaporation in vacuo 7.1 g (60 %) of benzyloxy-methyl-2,3-dihydro-pyran-4-one as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.31 (m, 6H), 5.42 (dd, J = 6,1 Hz, 1H), 4.61 (d, J = 3 Hz, 1H), 4,57 (m, 1H), 3.70 (m, 2H), 2.74 (dd, J = 17 Hz, 14 Hz, 1H), 2.41 (ddd, J = 17 Hz, 2 Hz, 1 Hz, 1H).

The above 2,3-dihydro-pyran-4-one (7.1 g, 0.032 mol) and 10 % palladium on carbon (0.4 g) in ethyl acetate (50 ml) were placed in a Parr bomb shaker and hydrogenated at 30 psi. The reaction mixture was shaken for 2 h, at which time TLC analysis (methanol/dichloromethane 1:9) indicated the reaction was complete. The reaction mixture was filtered through a pad of Celite and the volatiles evaporated in vacuo. The residue was

subjected to flash column chromatography using ethyl acetate as eluant. Pure fractions were collected affording after evaporation in vacuo 3.0 g (75 %) of 2-hydroxymethyl-tetrahydro-pyran-4-one as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 - 4.29 (m, 1H), 3.77 - 3.66 (m, 3H), 3.61 - 3.54 (m, 1H), 2.65 - 2.43 (m, 2H), 2.34 - 2.27 (m, 2H), 2.04 (bs, 1H, CH_2OH).

The above tetrahydro-pyran-4-one (1.90 g, 0.015 mol), *tert*-butyl cyanoacetate (2.7 g, 0.019 mol), sulfur (0.51 g, 0.016 mol) and morpholine (2.55 ml, 0.03 mol) were dissolved in absolute ethanol (20 ml), and heated to 50 °C for 16 h. The reaction mixture was cooled, filtered and the filtrate evaporated in vacuo. The resultant oil was dissolved in ethyl acetate (50 ml), washed with water (2 x 50 ml), brine (2 x 50 m) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was subjected to flash column chromatography using ethyl acetate/hexanes (1:1) as eluant. Pure fractions were collected affording after evaporation in vacuo 3.7 g (90 %) of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (s, 2H), 3.80 - 3.67 (m, 3H), 2.77 - 2.72 (m, 1H), 2.57 - 2.53 (m, 1H), 1.54 (s, 9H).

The above carboxylic acid *tert*-butyl ester (1.0 g, 3.5 mmol), 4-chloro-1,3-dioxo-1,3-dihydro-isoindol (0.67 g, 3.7 mmol) and triphenylphosphine (1.01 g, 3.9 mmol) were dissolved in dry tetrahydrofuran (30 ml) and cooled to 0 °C under a nitrogen atmosphere. Diisopropyl azodicarboxylate (DIAD) (0.62 ml, 3.9 mmol) was added dropwise at 0 °C and the solution allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and the resultant solid dissolved in ethyl acetate (50 ml). The organic phase was washed with brine (3 x 50 ml), dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexanes (1:3) as eluant. Semi pure fractions were collected affording after evaporation in vacuo 0.7 g which was trituated with diethyl ether. The solid was filtered off and

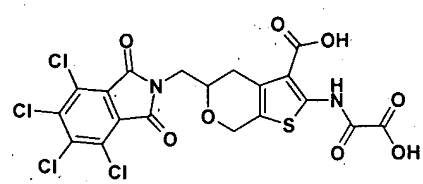
washed with diethyl ether and dried in vacuo affording 0.13 g (27 %) of 2-amino-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid. The filtrate was evaporated in vacuo. The residue (0.48 g) was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexanes (1:3) as eluant. Pure fractions were collected affording after evaporation in vacuo an additional 0.36 g (23 %) of 2-amino-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

To the above 4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert* butyl ester (0.36 g, 0.8 mmol) dissolved in tetrahydrofuran (20 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.31 g, 1.6 mmol) in tetrahydrofuran (3.4 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature for 18 hours. An additional portion of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.3 g, 1.6 mmol) in tetrahydrofuran (2 ml) was added. The reaction mixture was allowed to stir at room temperature for an additional 60 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with brine (3 x 50 ml) dried (Na_2SO_4), filtered and the organic phase evaporated in vacuo. The residue (0.5 g) was purified by column chromatography (300 ml silicagel) using a mixture of ethyl acetate/heptane (1:2) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.36 g (80 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

The above di-*tert*-butyl ester (0.3 g, 0.52 mmol) was dissolved in dichloromethane (1.2 ml) and trifluoroacetic acid (0.5 ml) was added. The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue trituated with a mixture of diethyl ether and heptane (1:1) (5 ml). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 200 mg (69 %) of the title compound as a solid.

M.p.: > 250 °C
Calculated for $C_{19}H_{13}N_2ClO_8S$;
C, 49.09 %; H, 2.82 %; N, 6.03 %. Found:
C, 48.79 %; H, 2.79 %; N, 5.89 %.

EXAMPLE 2



5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4 ml scintillating vial, a solution of tetrachloro phthalimide (148 mg, 0.52 mmol) in N,N-dimethylformamide (2.0 ml) was heated to 100°C for 10 minutes and treated with potassium hydride (55 mg, 0.48 mmol, 35 % w/w dispersion in mineral oil). The resulting mixture was stirred until gas generation ended, 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzenesulfonyl-oxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (151 mg, 0.25 mmol) and 18-crown-6 ether (31 mg, 0.12 mmol) were added. The solution was flushed with nitrogen gas before being stirred at 80°C for 25 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (5:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 39 mg (23 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 4.80 (d, *J* = 16, 1H), 4.67 (d, *J* = 14, 1H), 4.14-3.99 (m, 2H), 3.84(d, *J* = 9, 1H), 2.99 (d, *J* = 17, 1H), 2.70 (dd, *J* = 17, 5, 1H), 1.60 (s, 9H), 1.56 (s, 9H).

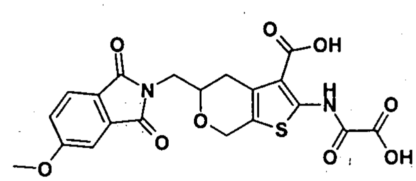
HPLC (254.4 nm) R_t=5.80 min, 95%.

In a 25 ml round bottom flask, 2-(*tert*-butoxyoxalyl-amino)-5-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (39 mg, 0.06 mmol) was dissolved in 20 % trifluoroaceetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. A precipitate was filtered off and washed with diethyl ether, affording after drying 29 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 4.76 (d, J = 16, 1H), 4.59 (d, J = 14, 1H), 4.0-3.6 (m partially obscured by water, 3H), 3.1 (d partially obscured by water, J = 17, 1H), 2.61 (dd partially obscured by DMSO, J = 20, 11, 1H).

HPLC (254.4 nm) R_t=4.15 min, 75 %.

EXAMPLE 3



5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxyphthalic acid (0.25 g, 1.37 mmol) in anhydrous N,N-dimethylformamide (3 ml) under nitrogen was added sodium hydride (0.22 g, 5.48 mmol). The solution was stirred for 5 minutes and then methyl iodide (0.68 ml) was added and continued stirring for 3 hours. Several drops of water were added to quench the reaction and the mixture was concentrated in vacuo. The crude material was partitioned between ethyl acetate (40 ml) and water (10 ml). The layers were

separated and the organic layer washed with brine (2 x 10 ml), dried(Na_2SO_4), filtered and the solvent evaporated in vacuo. The resulting oil was dissolved in methanol (8 ml) and 1N sodium hydroxide (4 ml) was added. The reaction was stirred at ambient temperature for 24 h., after which LC-MS indicated only partial hydrolysis. The material was reconstituted in methanol (5 ml) and treated with of sodium hydroxide (0.12 g, 3.0 mmol) dissolved in water (1 ml). The reaction mixture was stirred for 48 h., at which time a precipitate had formed. The mixture was acidified with 6N hydrochloric acid until pH = 1, causing the solution to become homogeneous. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate (30 ml) and 0.5N hydrochloric acid (10 ml). The layers were separated and the organic layer concentrated in vacuo to give 100 mg (51 %) of 4-methoxy-phthalic acid as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (d, J = 8, 1H), 7.10-7.06 (m, 2H), 3.87 (s, 3H).

LC-MS: R_t=1.45 min, $[M+H]^+$ = 197.1

A solution of 4-methoxy-phthalic acid (0.10 g, 0.51 mmol), 1-hydroxy-benzotriazole (0.15 g, 1.1 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.22 g, 1.1 mmol), and triethylamine (0.35 ml, 2.5 mmol) was prepared in distilled acetonitrile (4 ml) under nitrogen. 2-Amino-5-aminomethyl-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.11 g, 0.39 mmol) was added in small portions and the reaction was stirred at ambient temperature for 18 h., and then concentrated in vacuo. The crude mixture was diluted in ethyl acetate (30 ml) and washed with 1% hydrochloric acid (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 10 % mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 54 mg (31 %) of 2-amino-5-

(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8, 1H), 7.32 (s, 1H), 7.14 (d, J = 8, 1H), 4.62-4.48 (m, 2H), 4.00-3.72 (m, 3H), 3.91 (s, 3H), 2.86 (d, J = 17, 1H), 2.55 (dd, J = 17 , 10, 1H), 1.49 (s, 9H).

To a solution of the above 2-amino-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (54 mg, 0.12 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.25 g, 0.36 mmol) and triethylamine (50 μl, 0.36 mmol). The reaction was stirred for 4 h., concentrated in vacuo and the residue reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic phase was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5% mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 56 mg (81%) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.75 (d, J = 8, 1H), 7.32 (d, J = 2 , 1H), 7.15 (dd, J = 8, 2, 1H), 4.78 (d, J = 15, 1H), 4.65 (d, J = 15, 1H), 4.03-3.75 (m, 3H), 3.91 (s, 3H), 2.95 (d, J = 17, 1H), 2.66 (dd, J = 17, 9 , 1H), 1.58 (s, 9H), 1.54 (s, 9H).
APCI-MS: $[M+H]^+$ = 574

The above 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (55 mg, 0.096 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction

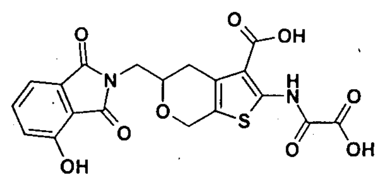
was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 17 mg (40%) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.81 (d, J = 8 , 1H), 7.40 (d, J = 2, 1H), 7.31 (dd, J = 8 , 2, 1H), 4.75 (d, J = 15, 1H), 4.56 (d, J = 15, 1H), 3.92 (s, 3H), 3.91-3.69 (m, 3H), 2.98 (d, J = 17, 1H), 2.57 (dd, J = 17, 9, 1H).

APCI-MS: $[M-H]^-$ = 459

HPLC (254.4nm): R_t=3.36 min, 98%

EXAMPLE 4



5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was prepared in a similar way as described in Example 1.

To a solution of the above benzylether (0.7 g, 1.08 mmol) in ethyl acetate (50 ml) was added 10 % palladium on carbon (0.2 g). The mixture was hydrogenated at 1 atm. for 5 h, filtered and the volatiles evaporated in vacuo. The residue (0.6 g) was purified by column chromatography (500 ml silicagel) using a mixture of ethyl acetate/heptane (1:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.4 g (67 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

TLC: R_f = 0.2 (ethyl acetate/heptane 1:1)

The above di-*tert*-butyl ester (0.4 g, 0.72 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue triturated with diethyl ether (5 ml). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 230 mg (72 %) of the title compound as a solid.

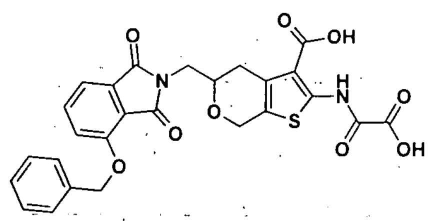
M.p.: > 250 °C;

Calculated for $C_{19}H_{14}N_2O_9S$, 0.5 x H_2O;

C, 50.11 %; H, 3.32 %; N, 6.15 %. Found:

C, 50.06 %; H, 3.17 %; N, 5.98 %.

EXAMPLE 5



5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

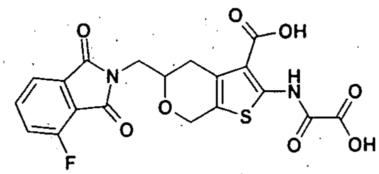
5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.7 g, 1.08 mmol) (prepared in a similar way as described in Example 1) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue triturated with diethyl ether (25 ml). The precipitate was filtered off, washed with diethyl ether and dried in vacuo at 50 °C for 3 hours which afforded 400 mg (69 %) of the title compound as a solid..

M.p.: 194 - 196 °C;

Calculated for $C_{26}H_{20}N_2O_9S$, 1 x H_2O, 0.6 x CF_3COOH;

C, 52.44 %; H, 3.66 %; N, 4.50 %. Found:
C, 52.33 %; H, 3.65 %; N, 4.62 %.

EXAMPLE 6

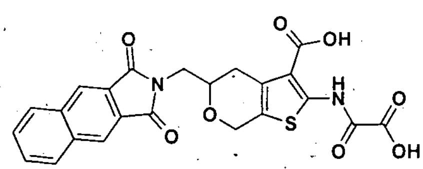


5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Prepared in a similar way as described in Example 1.

M.p.: > 250 °C;
Calculated for $C_{19}H_{13}FN_2O_8S$, 1 x H_2O;
C, 48.93 %; H, 3.24 %; N, 6.01 %. Found:
C, 48.90 %; H, 3.15 %; N, 5.86 %.

EXAMPLE 7



5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4-ml scintillating vial, a solution of benzo[*f*]isoindole-1,3-dione (145 mg, 0.74 mmol) in N,N-dimethylformamide (2.0 ml) was treated with potassium hydride (55 mg, 0.48 mmol, 35 % w/w dispersion in mineral oil).

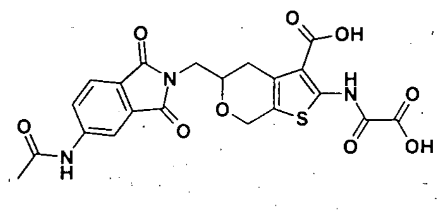
The resulting mixture was stirred until gas generation ended and the resulting precipitate was filtered off and washed with dichloromethane which afforded 121 mg (69 %) of benzo[*f*]isoindole-1,3-dione potassium salt as a solid.

^{1}H NMR (300 MHz, D_2O) δ 8.00-7.87 (m, 4H), 7.62 (s, 2H).

In a 4 ml scintillating vial, the above potassium salt (121 mg, 0.5 mmol) in N,N-dimethylformamide (1.5 ml) was treated with 18-crown-6 ether (34 mg, 0.13 mmol) and 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (148 mg, 0.25 mmol). The solution was flushed with nitrogen gas before being stirred at 80 °C for 7 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of ethyl acetate/dichloromethane (1:49) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 85 mg (57 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-benzo[*f*]isoindole-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.52 (s, 1H), 8.37 (s, 2H), 8.08 (m, 2H), 7.72 (m, 2H), 4.84-4.65 (m, 2H), 4.16-3.90 (m, 3H), 3.02 (d, J = 17, 1H), 2.73 (dd, J = 17, 10, 1H), 1.61 (s, 9H), 1.58 (s, 9H).

In a 25 ml round bottom flask the above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-benzo[*f*]isoindole-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (85 mg, 0.14 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. The precipitate was filtered off and washed with diethyl ether, affording after drying 62 mg (90 %) of the title compound as a solid.
^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.02 (s, 2), 4.81-4.59 (m, 2H), 3.97-3.81 (m partially obscured by water, 3H), 3.08 (d, J = 18, 1H), 2.74-2.53 (m partially obscured by DMSO, 1H).

EXAMPLE 8



5-(5-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of N-(1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-acetamide (51 mg, 0.25 mmol) in N,N-dimethylformamide (1.5 ml) under nitrogen at room temperature was added potassium hydride (35 wt.% dispension in mineral oil, 29 mg, 0.25 mmol). The solution was stirred at room temperature for 3 hours. A solid precipitated during this period. 2-(*tert*-Butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (100 mg, 0.17 mmol) was added to the suspension and the solution was stirred at 80 °C for 12 h. The solvent was evaporated in vacuo, the resulting residue purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25%) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 50 mg (50 %) of 5-(5-acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid. ^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 8.03 (d, 1H, J = 1.5 Hz), 7.91 (dd, 1H, J = 7.8, 1.8 Hz) 7.83 (d, 1H, J = 8.1 Hz), 7.45 (s, 1H), 4.80 (d, 1H, J = 16 Hz), 4.66 (d, 1H, J = 16 Hz), 4.03 (m, 2H), 3.83 (q, 1H, J = 15 Hz), 2.98 (d, 1H, J = 9 Hz), 2.64-2.78 (m, 1H), 2.27 (s, 3H), 1.62 (s, 9H), 1.57 (s, 9H).

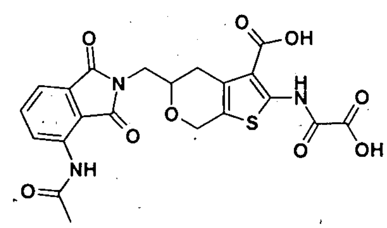
To a mixture of trifluoroacetic acid/dichloromethane (2 ml, 1:1) at room temperature was added the above 5-(5-acetylamino-1,3-dioxo-1,3-

dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (40 mg, 0.067 mmol). The solution was stirred for 5 h. at which time the solvent was removed in vacuo. The residue was washed with dichloromethane, filtered off, and dried in vacuo which afforded 23 mg (70 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 10.58 (s, 1H), 8.21 (s, 1H) 7.84 (s, 2H), 4.76 (d, 1H, J = 15 Hz), 4.58 (d, 1H, J = 15 Hz), 3.80-4.00 (m, 3H), 3.00 (d, 1H, J = 17 Hz), 2.58-2.73 (m, 1H), 2.13 (s, 3H).

MS: 488 (M+1).

EXAMPLE 9



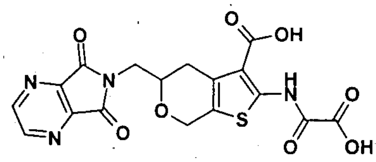
5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described for Example 8.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 9.76 (s, 1H), 8.45 (d, 1H, J = 8.4 Hz) 7.79 (t, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 8.4 Hz), 4.77 (d, 1H, J = 15 Hz), 4.58 (d, 1H, J = 15 Hz), 3.68-3.94 (m, 3H), 3.02 (d, 1H, J = 16 Hz), 2.55-2.78 (m, 1H), 2.20 (s, 3H).

MS: 488 (M+1).

EXAMPLE 10



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4-ml scintillating vial, a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (148 mg, 0.5 mmol) in tetrahydrofuran (1.0 ml) was treated with a solution of pyrazine phthtalic acid anhydride (85 mg, 0.56 mmol) in tetrahydrofuran (1.0 ml) and N,N-dimethylformamide (0.5 ml). The reaction mixture was allowed to stir at room temperature for 1 h. Diisopropylethylamine (220 μl, 0.13 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (121 mg, 0.6 mmol) were then added. The reaction mixture was shaken vigorously for 10 seconds before being stirred at room temperature for 14 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of dichloromethane/ethyl acetate (3:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 25 mg (12 %) of the 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid. ^1H NMR (300 MHz, $CDCl_3$) d 8.97 (s, 2H), 4.62-4.49 (m, 2H), 4.21-4.04 (m, 2H), 3.94 (dd, J = 14, 4, 1H), 2.91 (d, J = 17, 1H), 2.63 (dd, J = 17, 10, 1H), 1.68 (s, 9H).

In a 4 ml scintillating vial a solution of the above 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (25 mg, 0.06 mmol) in tetrahydrofuran (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.36 mmol). After stirring for 3 hours at room temperature the reaction solution was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 31 mg (95 %) of 2-(*tert*-butoxyoxalyl-

amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.96 (s, 2H), 4.80-4.61 (m, 2H), 4.21-4.04 (m, 2H), 3.96 (dd, J = 14, 4, 1H), 3.03 (d, J = 16, 1H), 2.70 (dd, J = 17, 10, 1H), 1.60 (s, 9H), 1.59 (s, 9H).

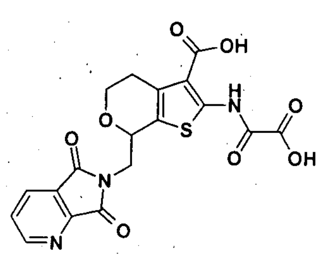
In a 25 ml round bottom flask the above 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester, (31 mg, 0.06 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. A precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.02 (s, 2), 4.81-4.59 (m, 2H), 3.97-3.81 (m partially obscured by water, 3H), 3.08 (d, J = 18, 1H), 2.74-2.53 (m partially obscured by DMSO, 1H).

HPLC (254.4 nm) R_t=2.97 min, 89%.

MS (APCI$^-$) [M-H] 432.4

EXAMPLE 11



7-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

A solution of furo[3,4-b]pyridine-5,7-dione (86.1 mg, 0.58 mmol) and of 2-(*tert*-butoxyoxalyl-amino)-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (194 mg, 0.47 mmol) in acetonitrile (2.0 ml) was stirred for 10 min. at room temperature. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (89.2 mg, 0.564 mmol) and triethylamine (198 μl, 1.41 mmol) were added and the mixture was stirred at room temperature for 20 h. The volatiles were removed <u>in vacuo</u> and the crude product dissolved in dichloromethane (60 ml) and washed with water (3 x 30ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removal <u>in vacuo</u>. The residue (338 mg) was purified by column chromatography on silica gel utilizing a mixture of hexane/ethyl acetate (90/10 to 50/50) as gradient which afforded after evaporation of the solvent <u>in vacuo</u> 85 mg (33 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihyd-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ 9.00 (d, J = 4.8, 1H), 8.21 (d, J = 7.5, 1H), 7.64 (dd, J = 4.8, J = 6.8, 1H), 5.12 (d, J = 7.2, 1H), 4.24-4.1 (m, 2H), 3.97-3.91 (m, 1H), 3.75 (m, 1H), 2.90 (m, 1H), 1.29 (s, 9H), 1.27 (s, 9H).

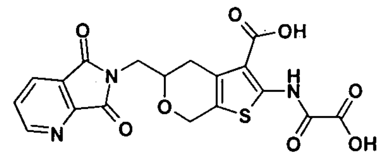
MS: 544 (M+1).

The above 2-(*tert*-butoxyoxalyl-amino)-7-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihyd-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (47.4 mg, 0.087 mmol) was stirred in 50% trifluoroacetic acid in dichloromethane (2 ml) at room temperature for 5 h. The solvent was removed <u>in vacuo</u> and the residue was washed with diethyl ether (4 x 3.0 ml) and dried which afforded 26.5 mg (70 %) of the <u>title compound</u> as a solid.

^{1}H NMR (400MHz, CD_3OD): δ 8.96 (d, J = 5, 1H), 8.30 (d, J = 7.6, 1H), 7.79 (dd, J = 5.2, J = 5.2, 1H), 5.10 (d, J = 6.4, 1H), 4.16 (m, 2H), 3.96 (dd, J = 3.2, J = 3.6, 1H), 3.78 (m, 1H), 2.95 (m, 2H).

MS: 432 (M+1).

EXAMPLE 12



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Pyrrolo[3,4-b]pyridine-5,7-dione (74.2 mg, 0.5 mmol) was stirred with sodium hydride (60% dispersion in mineral oil, 20.04 mg, 0.5 mmol) in N,N-dimethylformamide (4.0 ml) at room temperature under inert atmosphere. 2-(*tert*-Butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (198 mg, 0.33 mmol) was added to the sodium salt formed and the reaction was stirred at 80 °C for 20 h. The solvent was removed in vacuo and the crude product was purified by preparative TLC (hexane:ethyl acetate 50:50) which afforded 58 mg (21 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (d, J = 5, 1H), 8.20 (d, J = 7.5, 1H), 7.65 (dd, J = 5, J = 5, 1H), 4.80 (d, J = 14.7, 1H), 4.66 (d, J = 14.7, 1H), 4.10 (m, 2H), 3.91 (d, J = 13.2, 1H), 3.02 (d, J = 16.5, 1H), 2.70 (m, 1H), 1.61 (s, 9H), 1.58 (s, 9H).

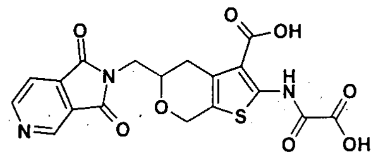
MS: 544 (M+1).

The above 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (46.4 mg, 0.09 mmol) was stirred in 20 % trifluoroacetic acid in dichloromethane (3.0 ml) at room temperature for 2 h. The volatiles were removed in vacuo and the residue was washed with diethyl ether (5 x 3 ml) affording 37 mg (99 %) of the title compound as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.96 (d, J = 5.4, 1H), 8.20 (d, J = 7.7, 1H), 7.64 (m, 1H), 4.77 (d, J = 14.7, 1H), 4.61 (d, J = 14.7, 1H), 4.07 (m, 2H), 3.86 (d, J = 10.5, 1H), 3.12 (d, J = 17.4, 1H), 2.77-2.68 (m, 2H).

MS: 432 (M+1).

EXAMPLE 13



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of pyrrolo[3,4-c]pyridine-1,3-dione (74 mg, 0.50 mmol) in N,N-dimethylformamide (1 ml) under nitrogen at room temperature was added potassium hydride (35 wt.% dispersion in mineral oil, 57 mg, 0.50 mmol). The solution was stirred at room temperature for 3 hours. A solid precipitated during this period. 18-Crown-6 (33 mg, 0.13 mmol) and 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (150 mg, 0.25 mmol) were then added. The solution was stirred at 80°C for 12 h and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25%) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 93 mg (68 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 12.49 (s, 1H), 9.20 (s, 1H), 9.11 (d, 2H, J = 4.8 Hz) 7.80 (d, 2H, J = 4.8 Hz), 4.80 (d, 1H, J = 16 Hz), 4.66 (d, 1H, J = 16 Hz), 4.00-4.18 (m, 2H), 3.70-3.95 (m, 1H), 3.01 (d, 1H, J = 17 Hz), 2.64-2.78 (m, 1H), 1.60 (s, 9H), 1.59 (s, 9H).

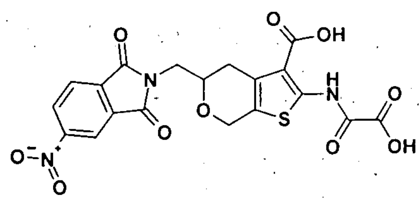
To a mixture of trifluoroacetic acid/dichloromethane (1 ml, 1:1) at room temperature was added the above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (29 mg, 0.053 mmol). The solution was stirred for 5 h. and the solvent evaporated in vacuo. The

residue was washed with dichloromethane afford after drying in vacuo 22 mg (96 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 9.15 (s, 1H), 9.11 (d, 2H, J = 4.8 Hz) 7.92 (d, 2H, J = 4.8 Hz), 4.76 (d, 1H, J = 15 Hz), 4.58 (d, 1H, J = 16 Hz), 3.75-4.00 (m, 4H), 3.04 (d, 1H, J = 17 Hz).

MS: 432 (M+1).

EXAMPLE 14



5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4-ml scintillating vial, a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (58 mg, 0.2 mmol) in tetrahydrofuran (2.0 ml) was treated with 4-nitrophthalic acid (63 mg, 0.3 mmol), diisopropylethylamine (190 μl, 1.1 mmol), and 1,3-diisopropylcarbodiimide (120 μl, 0.77 mmol). The reaction mixture was shaken vigorously for 10 seconds before being stirred at 50 °C for 43 hours and at room temperature for 20 h. The solution was diluted with ethyl acetate (25 ml), washed with 0.5N aqueous hydrochloric acid (25 ml), saturated aqueous sodium bicarbonate (25 ml), and brine (25 ml). The organic layer was dried($MgSO_4$), filtered and the solvent evaporated in vacuo. Crude 2-amino-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained as a solid and used immediately in the next step.

In a 4 ml scintillating vial a solution of the above crude 2-amino-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester in dichloromethane (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (147 mg, 0.75

mmol). After stirring for 2 h. at room temperature the reaction mixture was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo which afforded 30 mg (26 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

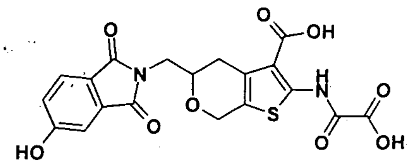
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.71 (s, 1H), 8.64 (d, J = 8, 1H), 8.08 (d, J = 9, 1H), 4.79 (d, J = 14, 1H), 4.65 (d, J = 14, 1H), 4.21-3.97 (m, 2H), 3.89 (d, J = 12, 1H), 3.01 (d, J = 16, 1H), 2.83-2.61 (m, 1H), 1.63 (ds, 18H).

In a 25 ml round bottom flask, the above 2-(*tert*-butoxyoxalyl-amino)-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (30 mg, 0.05 mmol) was dissolved in a mixture of 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring of 24 h. A precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.63 (d, J = 8, 1H), 8.15 (d, J = 8, 1H), 4.76 (d, J = 16, 1H), 4.57(d, J = 16, 1H), 4.42-3.74 (m partially obscured by water, 3H), 3.04 (d partially obscured by water, J = 16, 1H), 2.61 (m partially obscured by DMSO, 1H).

HPLC (254.4 nm) R_t=3.40 min, 86%.
MS (APCI$^+$) [M+H] 407.6

EXAMPLE 15



5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxyphthalic acid (0.45 g, 2.47 mmol) in anhydrous N,N-dimethylformamide (5 ml) under nitrogen was added chloromethyl methyl ether (1.13 ml, 14.8 mmol) and diisopropylethylamine (2.6 ml, 14.8 mmol). The reaction was stirred at ambient temperature for 18 h. and then concentrated in vacuo. The crude material was partitioned between ethyl acetate (50 ml) and water (15 ml). The layers were separated, the organic layer washed with water (3 x 10 ml), brine (2 x 10 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The resulting oil was dissolved in ethanol (5 ml) and sodium hydroxide (0.12 g, 7.4 mmol) dissolved in water (1 ml) was added to the reaction. The solution was stirred at ambient temperature for 48 h. and then concentrated in vacuo affording 4-methoxymethoxy-phthalic acid di-sodium salt which was used without purification.

^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (d, J = 8, 1H), 7.06 (d, J = 3, 1H), 6.89 (dd, J = 8, 3, 1H), 5.18 (s, 2H), 3.42 (s, 3H).

A solution of 4-methoxymethoxy-phthalic acid di-sodium salt (0.19 g, 0.70 mmol), 1-hydroxybenzotriazole (0.2 g, 3.6 equiv.), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.28 g, 3.6 equiv.), and triethylamine (0.33 ml, 6 equiv.) was prepared in distilled acetonitrile (5 ml) under nitrogen. The mixture was stirred for 5 minutes before 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (115 mg, 0.40 mmol) was added in small portions. The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo. The crude mixture was diluted with ethyl acetate (30 ml) and washed with 1% hydrochloric acid (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel

chromatography using a gradient of ethyl acetate/dichloromethane (5 to 10% gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 44 mg (23 %) of 2-amino-5-(5-methoxy-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8, 1H), 7.48 (d, J = 2, 1H), 7.27 (dd, J = 8, 2, 1H), 5.26 (s, 2H), 4.60-4.46 (m, 2H), 3.99-3.71 (m, 3H), 3.47 (s, 3H), 2.85 (d, J = 17, 1H), 2.55 (dd, J = 17, 9, 1H), 1.48 (s, 9H).

To a solution of the above 2-amino-5-(5-methoxy-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (44 mg, 0.095 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (56 mg, 0.29 mmol) and triethylamine (26 μl, 0.19 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The resulting solution was dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 35 mg (63 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.75 (d, J = 8, 1H), 7.49 (d, J = 2, 1H), 7.28 (dd, J = 8, 2, 1H), 5.26 (s, 2H), 4.77 (d, J = 15, 1H), 4.64 (d, J = 15, 1H), 4.03-3.74 (m, 3H), 3.47 (s, 3H), 2.95 (d, J = 17, 1H), 2.65 (dd, J = 17, 9, 1H), 1.58 (s, 9H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 603.7

The above 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (35 mg, 0.058 mmol) was dissolved in a

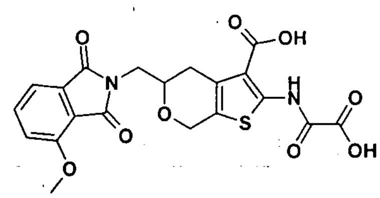
mixture of 50 % trifluoroacetic acid/dichloromethane (2.5 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 20 mg (77 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 10.97 (s, 1H), 7.72 (d, J = 8, 1H), 7.18 (s, 1H), 7.10 (d, J = 8, 1H), 4.74 (d, J = 15, 1H), 4.58 (d, J = 15, 1H), 3.96-3.62 (m, 3H), 2.99 (d, J = 17, 1H), 2.60-2.50 (m, 1H, partially obscured by DMSO).

APCI-MS: $[M-H]^-$ = 445.4

HPLC (254.4nm): R_t=2.92 min, 95%

EXAMPLE 16



5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (195 mg, 1.2 mmol) in anhydrous N,N-dimethylformamide (4 ml) under nitrogen was added sodium hydride (61 mg, 1.56 mmol). The solution was stirred for 15 minutes and then methyl iodide (0.37 ml, 6.0 mmol) was added. The reaction was stirred for 48 h. and then quenched with saturated ammonium chloride. The mixture was concentrated in vacuo, diluted in ethyl acetate (20 ml) and the organic phase washed with 1N hydrochloric acid (5 ml) and brine (3 x 5 ml). The organic layer was dried($MgSO_4$) and concentrated in vacuo. To the crude solid was added methanol causing a precipitate to form. The flask was cooled in an ice bath for 2 h. and the

solid filtered off, washed with methanol and dried in vacuo which afforded 0.1 g (47 %) of 4-methoxy-isobenzofuran-1,3-dione as a solid.
^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (t, J = 8, 1H), 7.61 (d, J = 8, 1H), 7.58 (d, J = 8, 1H), 3.99 (s, 3H).
APCI-MS: $[M+H]^+$ = 179.1

A solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (122 mg, 0.43 mmol, prepared as described in Example 17) and 4-methoxy-isobenzofuran-1,3-dione (92 mg, 0.52 mmol) was prepared in distilled tetrahydrofuran (4 ml) under nitrogen. 1-hydroxybenzotriazole (87 mg, 0.65 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (123 mg, 0.65 mmol), and triethylamine (0.29 ml, 2.15 mmol) were added. The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo. The crude mixture was diluted with ethyl acetate (25 ml) and washed with 1N hydrochloric acid (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 0.18 g (94 %) of 2-amino-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, J = 7, 1H), 7.43 (d, J = 7 , 1H), 7.19 (d, J = 7, 1H), 4.59-4.46 (m, 2H), 4.06-3.72 (m, 3H), 4.00 (s, 3H), 2.87-2.81 (m, 1H), 2.60-2.51 (m, 1H), 1.48 (s, 9H).

To a solution of the above 2-amino-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.18 g, 0.42 mmol) in distilled dichloromethane (5 ml) under nitrogen was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.25 g, 1.26 mmol) and triethylamine (0.23 ml, 1.68 mmol). The reaction was stirred for 12 h., concentrated in vacuo and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The resulting solution was dried(Na_2SO_4), filtered, and the solvent evaporated

in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 10 % gradient). Pure fractions were collected and the solvent evaporated in vacuo to give 195 mg (81 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.65 (t, J = 7, 1H), 7.43 (d, J = 7, 1H), 7.19 (d, J = 7, 1H), 4.77 (d, J = 15, 1H), 4.63 (d, J = 15, 1H), 4.04-3.75 (m, 3H), 4.00 (s, 3H), 2.94 (d, J = 17, 1H), 2.65 (dd, J = 17, 10, 1H), 1.58 (s, 9H), 1.53 (s, 9H).

LC-MS: R_t=4.17 min, $[M+H]^+$ = 573.2

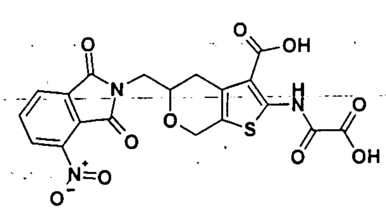
The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.15 g, 0.26 mmol) was dissolved in a mixture of 50 % trifluoroacetic acid/dichloromethane (5 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 100 mg (83 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 7.79 (t, J = 8, 1H), 7.48 (d, J = 8, 1H), 7.42 (d, J = 8, 1H), 4.74 (d, J = 15, 1H), 4.56 (d, J = 15, 1H), 3.95 (s, 3H), 3.91-3.79 (m, 2H), 3.69-3.63 (m, 1H), 2.98 (d, J = 17, 1H), 2.57 (dd, J = 17, 10, 1H).

LC-MS: R_t=1.26 min, $[M+H]^+$ = 461.0

HPLC (254.4nm): R_t=3.10 min, 100 %

EXAMPLE 17



5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 50-ml round-bottom flask, a suspension of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (2.00 g, 4.8 mmol) in absolute ethanol (20 ml) was flushed with nitrogen and sealed with a rubber septum. Hydrazine (0.5 ml, 15.9 mmol) was added, followed by an additional portion of absolute ethanol (20 ml) at room temperature. The reaction mixture was heated to 80 °C for 3.5 h., then allowed to stir at room temperature for 14 h. The precipitate was filtered off and washed with absolute ethanol. The filtrate was concentrated in vacuo leaving an oil, which was dissolved in dichloromethane (30 ml) and refiltered. The solvent was evaporated in vacuo affording 1.2 g (86 %) of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) d 5.92 (s, 2H), 4.64 (s, 2H), 3.68-3.60 (m, 1H), 2.98-2.74 (m, 3H), 2.56-2.44 (m, 1H), 1.54 (s, 9H).

MS (APCI$^+$) [M+H] 285.3

In a 4-ml scintillating vial, a solution of the above 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (63 mg, 0.2 mmol) in tetrahydrofuran (2.0 ml) was treated with 3-nitro-phthalic acid (66 mg, 0.3 mmol), diisopropylethylamine (190 μl, 1.1 mmol), and 1,3-diisopropyl-carbodiimide (120 μl, 0.77 mmol). The reaction mixture was shaken vigorously for 10 seconds before being stirred at 50°C for 43 hours and at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate (25 ml) and washed with 0.5N aqueous hydrochloric acid (25 ml), saturated sodium bicarbonate (25 ml), and brine (25 ml). The organic layer was dried($MgSO_4$), filtered and the solvent evaporated in vacuo affording crude 2-amino-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

In a 4 ml scintillating vial a solution of the above crude 2-amino-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester in dichloromethane (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (147 mg, 0.75 mmol). After stirring for 2 h. at room temperature the reaction solution was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 30 mg (26%) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 5, 1H), 8.11 (d, J = 6, 1H), 7.94 (t, J = 8, 1H), 4.80 (d, J = 14, 1H), 4.67 (d, J = 15, 1H), 4.16-3.97 (m, 3H), 3.88 (d, J = 10, 1H), 3.01 (d, J = 16, 1H), 2.70 (dd, J = 16, 10, 1H), 1.62 (s, 9H), 1.59 (s, 9H).

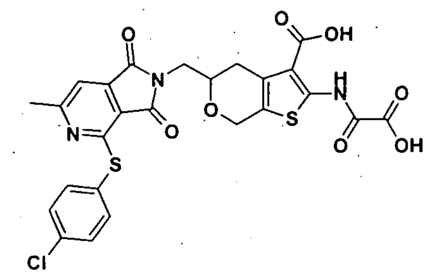
In a 25 ml round bottom flask, the above 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (30 mg, 0.05 mmol) was dissolved in a mixture of 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After standing for 24 h. a precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.32 (d, J = 9, 1H), 8.20 (d, J = 9, 1H), 8.07 (t, J = 9, 1H), 4.77 (d, J = 14, 1H), 4.59 (d, J = 16, 1H), 4.00-3.65 (m partially obscured by water, 3H), 3.04 (d partially obscured by water, J = 16, 1H), 2.63 (dd partially obscured by DMSO, J = 17, 13, 1H).

HPLC (254.4 nm) R_t= 3.33 min, 100%.

MS (APCI$^+$) [M+H] 391.6

EXAMPLE 18



5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Under a nitrogen atmosphere, 4-(4-chloro-phenylsulfanyl)-6-methyl-pyrrolo[3,4-c]-1,3-dione (914 mg, 3.0 mmol), tributylphosphine (1.66 ml, 4.5 mmol) and 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (855 mg, 3.0 mmol) were successively dissolved in dry benzene (90 ml). Solid azodicarboxylic dipiperidine (1.13 g, 4.5 mmol) was added under stirring at 0 °C to the solution. After stirring for 10 min, the reaction mixture was brought to room temperature and the stirring continued for 4 h. The mixture was cooled on ice, and additional portions of tributylphosphine (1.66 ml, 4.5 mmol) and azodicarboxylic dipiperidine (1.13 g, 4.5 mmol) were added. After stirring for 10 min, the reaction mixture was brought to room temperature and the stirring continued for 18 h. Heptane (30 ml) was added to the reaction and the precipitate filtered off (discard). After evaporation of the solvent the product was purified by flash chromatography to give 1.3 g (76 %) of 2-amino-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

Mp: 118 - 119° C;

^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.50 (s, 3H), 2.50-2.65 (m, 1H), 2.85- 2.95 (m, 1H), 3.75-3.85 (m, 1H), 3.95- 4.05, (m, 2H), 4.50- 4.15 (m, 2H), 5.95 (bs, 2H), 7.30 (s, 1H), 7.40 (d, 2H), 7.55 (d, 2H).

To an ice cooled solution of 2-amino-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (572 mg, 1 mmol) and dry triethylamine (2 ml) in dry tetrahydrofuran (10 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (588 mg, 3 mmol). After 10 min, the reaction mixture was brought to room temperature and the stirring continued for 18 h. The mixture was concentrated <u>in vacuo</u> and submitted to flash chromatography using a mixture of toluene/ethyl acetate (30:1) as eluant. Pure fraction were collected and the solvent evaporated <u>in vacuo</u> to give 360 mg (51 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

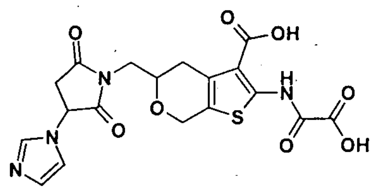
M.p.: 134 - 136° C;
^{1}H NMR ($CDCl_3$) δ 1.60 (s, 9H), 1.63 (s, 9H), 2.50 (s, 3H), 2.65-2.75 (m, 1H), 2.95- 3.05 (m, 1H), 3.75-3.90 (m, 1H), 4.00- 4.10, (m, 2H), 4.60- 4.85 (m, 2H), 7.30 (s, 1H), 7.40 (d, 2H), 7.55 (d, 2H), 12.50 (s, 1H).

To 2-(*tert*-butoxyoxalyl-amino)-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (324 g, 0.46 mmol) was added a mixture of trifluoroacetic acid (2.5 ml) and dichloromethane (7.5 ml). The mixture was stirred for 5 h, and added petroleum ether/ethyl acetate. The precipitate was isolated off and re-suspended in ethyl acetate. The <u>title compound</u> 136 mg (50 %) was isolated by filtration.

Mp: 239 - 240° C;
Calculated for $C_{25}H_{18}ClN_3O_8S_2$, 0.75 x H_2O;
C, 49.92 %; H, 3.27 %; N, 6.99 %. Found:
C, 49.83 %; H, 3.16 %; N, 6.85 %.

^1H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.65-2.75 (m, 1H), 2.95- 3.05 (m, 1H), 3.50-4.00 (m, 3H), 4.50- 4.90 (m, 2H), 7.50-7.68 (m, 5H), 12.30 (s, 1H).

EXAMPLE 19



5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.53 g, 1.86 mmol, prepared as described in Example 17) in tetrahydrofuran (10 ml) was added, maleic acid (0.24 g, 2.05 mmol) and diisopropylcarbodiimide (0.58 ml, 3.72 mmol). The reaction mixture was heated to reflux for 3 hours and then allowed to cool to room temperature over an 18 hour period. The solvent was stripped off in vacuo and the residue diluted into ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (2 x 50 ml), 1 % hydrochloric acid (2 x 20 ml), brine (3 x 50 ml), dried($MgSO_4$), filtered, and the solvent evaporated in vacuo affording an oil which was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (6:4) as eluant. Pure fractions (R_f=0.25) were collected and the solvent evaporated in vacuo to give 0.60 g (90 %) of 2-amino-5-(2,5-dioxo-2,5-dihydro-pyrrol-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 5.7, 1H), 6.63 (d, J = 5.4, 1H), 5.94 (bs, 2H), 4.67 (s, 2H), 3.93 (m, 1H), 3.82 (m, 2H), 2.89-2.83 (m, 1H), 2.69-2.60 (m, 1H), 1.54 (s, 9H).

MS: APCI (+): 365.2 (M+H);

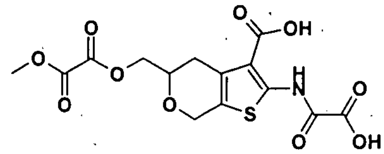
To a solution of the above 2-amino-5-(2,5-dioxo-2,5-dihydro-pyrrol-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (60 mg, 1.64 mmol) in tetrahydrofuran (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (50 mg, 2.46 mmol). The solution was stirred at room temperature for 48 h. The solvent was stripped off in vacuo and the resultant oil diluted in ethyl acetate (20 ml), washed with brine (3 x 25 ml), dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9) as eluant which afforded 25 mg (28 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(3-imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.94 (s, 1H), 5.92 (m, 1H), 5.22 (m, 1H), 4.68-4.53 (m, 2H), 4.00 (m, 3H), 3.71 (m, 1H), 3.47-3.38 (m, 1H), 3.03-2.87 (m, 1H), 2.61 (m, 1H), 1.60 (s, 9H), 1.54 (s, 9H).
MS: APCI (+): 561.2 (M+H).

To the above 2-(*tert*-butoxyoxalyl-amino)-5-(3-imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (25 mg, 0.05 mmol) was added a mixture of 20% trifluoroacetic acid in dichloromethane (2 ml). The reaction mixture was allowed to stir at room temperature for 2 h., at which time the mixture was concentrated in vacuo. The resultant solid was triturated with diethyl ether (2x) which afforded 13 mg (65 %) of the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 9.15 (s, 1H), 7.78 (s, 1H), 7.63 (m, 1H), 5.75 (m, 1H), 4.69 (m, 2H), 4.46 (m, 1H), 3.85 (m, 2H), 3.66 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 2.64 (m, 1H), 2.46 (m, 1H).
MS: ESI (-): 447.4 (M-H).

EXAMPLE 20



Oxalic acid 3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl

To a solution of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (8.0 g, 28 mmol) in dry tetrahydrofuran (50 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (27.51 g, 0.14 mol) and triethylamine (3.93 ml, 0.14 mol). The reaction mixture was stirred at room temperature for 20 h. The volatiles were removed in vacuo and the crude product was dissolved in ethyl acetate (300 ml) and washed with a saturated solution of sodium bicarbonate (3 x 100 ml), dilute hydrochloric acid (3 x 100 ml), water (3 x 100 ml) and brine (100 ml). The organic layer was dried($MgSO_4$), filtered and the solvent removed in vacuo affording a foam (16 g) which was purified on column chromatography on silica gel using a gradient of hexane/ethyl acetate (90:10 to 50:50 gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo which afforded 11 g (91 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 2H), 4.86 (d, J = 14.7, 1H), 4.77 (d, J = 14.4, 1H), 4.64 (m, 1H), 3.82-3.71 (m, 2H), 2.85 (d, J = 16.8, 1H), 2.68 (d, J = 10.5, 1H), 1.62 (s, 9H), 1.61 (s, 9H).

MS: 414 (M+1).

A solution of the above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester *tert*-butyl ester (8.3 g, 20.1 mmol) and potassium carbonate (1.7 g, 12.3 mmol) was stirred in methanol (80 ml) in presence of water (3 ml) at room temperature for 10 min., at which time TLC indicated reaction complete. Methanol was removed in vacuo and the crude product was dissolved in dichloromethane (300 ml) and washed with water (3 x 150 ml). The organic phase was dried($MgSO_4$), filtered and the solvent evaporated in

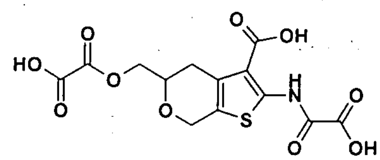
vacuo. The residue was purified on flash chromatography on silica gel using a gradient of hexane/ethyl acetate (90:10 to 50:50 gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.65 g (9 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 (d, J = 15, 1H), 4.78 (d, J = 15, 1H), 4.00 (s, 3H), 3.82-3.70 (m, 3H), 2.86 (d, J= 17, 1H), 2.66 (dd, J = 10.2, J = 10.5, 1H), 1.62 (s, 9H).
MS: 316 (M-55).

To a solution of the above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester (160 mg, 0.43 mmol) in dry tetrahydrofuran (3.0 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (420.4 mg, 2.15 mmol) and triethylamine (120 µl, 0.86 mmol). The resulting mixture was stirred at room temperature for 20 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel using a gradient of hexane/ethyl acetate (95:5 to 80:20 gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 173 mg (81 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester as a solid.
^{1}H NMR (300MHz, $CDCl_3$): δ 4.81 (dd, J = 14.7, J = 14.2, 2H), 4.40 (m, 2H), 4.00 (s, 3H), 2.96 (d, J = 15.3, 1H), 2.69 (dd, J = 10.8, J = 10.8, 1H), 1.61 (s, 9H), 1.57 (s, 9H).
MS: 388.3 (M-11).

The above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester (93.8 mg, 0.19 mmol) was stirred in 20 % trifluoroacetic acid in dichloromethane (2 ml) for 20 h. at room temperature. The solvent was removal in vacuo which afforded 73 mg (95 %) of the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD): δ 4.76 (d, *J* = 5.7, 2H), 4.18 (d, *J* = 4.8, 2H), 3.97 (s, 3H), 2.99 (d, *J* = 16.2, 1H), 2.65 (d, *J* = 10.8, 1H).
MS: 386 (M-1).

EXAMPLE 21



Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester

To a solution of a mixture of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1:4 estimated based on ^{1}H NMR) (200 mg, 0.70 mmol) and diisopropylethylamine (0.25 ml, 1.4 mmol) in dichloromethane (6.0 ml) cooled to 0 °C under nitrogen was added triethylchlorosilane (0.18 ml, 1.1 mmol). The solution was stirred at 0 °C for 5 min. and then stirred at room temperature for 15 min. The solution was washed with saturated sodium bicarbonate and brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/hexane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 42 mg (16 %) of 2-amino-5-triethylsilanyloxymethy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**1**) and 193 mg (69 %) of 2-amino-7-triethylsilanyloxy-methy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**2**).

(**1**) ^{1}H NMR ($CDCl_3$): δ 4.58 (m, 1H), 4.18-4.07 (m, 1H), 3.84 (dd, 1H, *J* = 9.6, 6.0 Hz), 3.80-3.70 (m, 1H), 3.60 (dd, 1H, *J* = 9.6, 7.8 Hz), 2.92-2.70 (m, 2H), 1.58 (s, 9H), 0.98 (t, 9 H, *J* = 7.8 Hz), 0.64 (q, 6H, *J* = 7.8 Hz);

(2) ^{1}H NMR ($CDCl_3$): δ 4.62 (s, 2H), 3.85-3.64 (m, 3H), 2.82 (dm, 1H, *J* = 15 Hz), 2.49 (dd, 1H, *J* = 15, 11 Hz), 1.58 (s, 9H), 0.98 (t, 9 H, *J* = 7.8 Hz), 0.64 (q, 6H, *J* = 7.8 Hz).

To a solution of 2-amino-7-triethylsilanyloxymethy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (6.0 g, 15 mmol) in dichloromethane (10 ml) cooled to 0 °C under the nitrogen was added a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (4.5 g, 18 mmol) in dichloromethane. The solution was stirred at 0 °C for 10 min. The reaction was quenched with water (1.0 ml). The solution was washed with brine and dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 10% mixture of ethyl acetate/hexane as eluant. Pure fractions of two compounds were collected and the solvent evaporated in vacuo affording 4.5 g (56 %) of 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**A**) as a solid and 50 mg of oxalic acid 3-(*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H- thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**B**) as a solid.

(**A**) ^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 4.85 (d, 1H, *J* = 12 Hz), 4.65 (d, 1H, *J* = 12 Hz), 3.90-3.60 (m, 3H), 2.94 (d, 1H, *J* = 15 Hz), 2.63 (dd, 1H, *J* = 15, 11 Hz), 1.63 (s, 9H), 1.61 (s, 9H), 0.98 (t, 9 H, *J* = 7.8 Hz), 0.64 (q, 6H, *J* = 7.8 Hz).

(**B**) ^{1}H NMR ($CDCl_3$): δ 12.47 (s, 1H), 4.82 (q, 2H, *J* = 14 Hz), 4.43 (m, 2H), 4.01 (m, 1H), 2.97 (d, 1H, *J* = 14 Hz), 2.69 (dd, 1H, *J* = 19, 9 Hz), 1.63 (s, 9H), 1.61 (s, 9 H), 1.58 (s, 9H).

To a solution of the above 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyl-oxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.5 g, 8.5 mmol) in tetrahydrofuran (10 ml) at room

temperature was added 0.5 N hydrochloric acid (2.0 ml). The solution was stirred at room temperature for 0.5 h. Ethyl acetate (100 ml) was added and the resulting solution was washed with saturated sodium bicarbonate, brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 10 % mixture of ethyl acetate/hexane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 3.0 g (84 %) of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 4.86 (d, 1H, J = 12 Hz), 4.60 (d, 1H, J = 12 Hz), 3.85-3.65 (m, 3H), 2.85 (d, 1H, J = 15 Hz), 2.65 (dd, 1H, J = 15, 11 Hz), 1.63 (s, 9H), 1.61 (s, 9H).

To a solution of the above 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (3.0 g, 7.1 mmol) in dichloromethane (10 ml) at room temperature was added pyridine (2.5 ml, 28.5 mmol) and 4-nitrobenzenesulfonyl chloride (4.7 g, 21.4 mmol). The solution was heated to 50 °C and stirred for 4.5 h. The solution was cooled to room temperature and washed with 0.5 N hydrochloric acid, saturated sodium bicarbonate, brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (0-100 %) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 3.6 g (84 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(4-nitrobenzenesulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 12.40 (s, 1H), 8.43 (d, 2H, J = 9.0 Hz), 8.17 (d, 2H, J = 9.0 Hz), 4.72 (d, 1H, J = 14 Hz), 4.64 (d, 1H, J = 14 Hz), 4.38-4.24 (m, 2H), 3.98-3.86 (m, 1H), 2.92 (d, 1H, J = 17 Hz), 2.65 (dd, 1H, J = 17, 12 Hz), 1.63 (s, 9H), 1.61 (s, 9H).

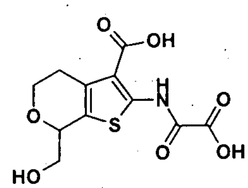
MS: 598 (M-1).

To a solution of 50 % trifluoroacetic acid/dichloromethane (1 ml) at room temperature was added oxalic acid 3-(*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H- thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (50 mg, 0.092 mmol). The solution was stirred for 3 hours. The solvent was removed in vacuo. The residue was washed with dichloromethane affording after filtration 25 mg (73 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 4.82 (d, 1H, J = 15 Hz), 4.68 (d, 1H, J = 15 Hz), 4.37 (s, 1H), 3.92 (m, 1H), 2.93 (d, 1H, J = 16 Hz), 2.60 (dd, 1H, J = 30, 10 Hz).

MS: 372 (M-1).

EXAMPLE 22



7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of 2-hydroxymethyl-tetrahydro-pyran-4-one (35 g, 0.27 mol), *tert*-butyl cyanoacetate (58.68 ml g, 0.4 mol), and sulphur (9.47 g, 0.3 mol) in absolute ethanol (400 ml) was added morpholin (47 ml, 0.54 mol), and the resulting mixture was heated to 45 °C for 16 h. The reaction mixture was cooled, filtered and the filtrate evaporated in vacuo. The resultant oil was dissolved in ethyl acetate (600 ml), washed with water (3 x 200 ml), brine (200 m), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue was crystallised from diethyl ether (100 ml) followed by addition of a mixture of diethyl ether and heptane (100 ml, 1:1). The precipitate was filtered off, washed with a mixture of diethyl ether and heptane (90 ml, 1:1) and dried in vacuo at 50 °C for 52 h affording 44.51 g of a mixture of 5 and 7 regioisomers according to NMR. The mixture of regioisomers (44.51 g) was suspended in diethyl ether (500 ml) and stirred

at room temperature for 96 h. and at reflux temperature for 2 h. After cooling to room temperature the precipitate was filtered off and washed with a mixture of diethyl ether and heptane (100 ml, 1:1) which afforded after drying in vacuo at 50 °C, 22.12 g (29 %) of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

All filtrates were pooled and evaporated in vacuo affording 55 g of a mixture of regioisomers. To 40.16 g (0.141 mol) of this regioisomer mixture dissolved in dichloromethane (450 ml) was added diisopropylethylamine (49.5 ml, 0.28 mol) and the mixture was cooled to 0 °C. Chlorothiethylsilane (38.2 ml, 0.23 mol) was added dropwise and the mixture was stirred for 10 minutes and for 15 minutes at room temperature. The reaction mixture was washed with saturated aqueous sodium carbonate (3 x 150 ml), brine (3 x 150 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (70.4 g) was partitioned into two portions which were subjected to flash chromatography (2 l silicagel) using a mixture of ethyl acetate/hexane (1:20) as eluant. Pure fractions of 2-amino-5-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-7-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester were collected. A fraction containing both isomers (18.84 g) was re-subjected to flash chromatography (2 l silicagel) using a mixture of ethyl acetate/hexane (1:20) as eluant. A total of 28.1 g (50 %) of 2-amino-5-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained. A total of 18.2 g (32 %) of 2-amino-7-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained.

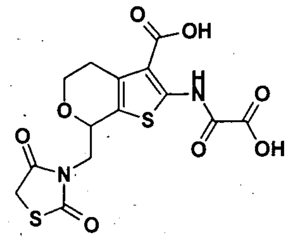
To the above 2-amino-7-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (18.2 g, 0.046 mol) dissolved in dichloromethane (200 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (17.9 g, 0.091 mol) in dichloromethane (30 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was evaporated in vacuo and

the residue was dissolved in ethyl acetate (100 ml) and washed with 1 N hydrochloric acid (3 x 50 ml), brine (3 x 75 ml), dried (Na_2SO_4), filtered and the organic phase evaporated in vacuo affording in quantitative yield 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester ester as a oil.

To a mixture of the above 7-triethylsilanyl ether (24.0 g, 0.046 mol) in tetrahydrofuran (100 ml) was added 1 N hydrochloric acid (18 ml) and the reaction mixture was stirred at room temperature for 1.5 h. Ethyl acetate (150 ml) was added and the reaction mixture was washed with saturated aqueous sodium carbonate (3 x 100 ml), brine (3 x 100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue was trituated with a mixture of diethyl ether and heptane (1:5) and the precipitate was filtered off, washed with heptane and dried in vacuo at 50 °C for 16 h affording 13.55 g (57 %) of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

The above 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (16 mg, 0.033 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (1 ml). The reaction was stirred at room temperature for 3 hours. The volatiles were evaporated in vacuo and the residue washed with dichloromethane which afforded 7 mg (73 %) of the title compound as a solid.
^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 4.62 (s, 1H), 4.12 (m, 1H), 3.62-3.78 (m, 2H), 3.40-3.52 (m, 1H), 2.83 (m, 2H).
MS: 300 (M-1).

EXAMPLE 23



7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.13 g, 0.46 mmol) in tetrahydrofuran (3 ml) was added triphenylphosphine (0.13 g, 0.51 mmol), and 2,4-thiazolidinedione (60 mg, 0.51 mmol). The reaction mixture was cooled to 0 °C and diisopropylazodicarboxylate (99 μl, 0.51 mmol) was added via syringe. The resultant mixture was stirred for 18 hours, gradually warming to room temperature. The volatiles were evaporated in vacuo and the resulting oil was diluted in ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to flash chromatography using a mixture of dichloromethane/methanol (9:1) as eluant. Pure fractions were collected (R_f=0.70) and the solvent evaporated in vacuo which afforded 89 mg (51 %) of 2-amino-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 2H), 4.82 (dm, 1H), 4.13-4.02 (bm, 2H), 3.99 (s, 2H), 3.75-3.67 (m, 1H), 3.60 (dd, 1H, *J* = 14, 3.3,), 2.81-2.74 (m, 2H), 1.54 (s, 9H).

MS: APCI (+): 385.6 (M+H).

To a solution of the above of 2-amino-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (89 mg) in tetrahydrofuran (5 ml) was added imidazol-1-yl-

oxo-acetic acid *tert*-butyl ester (79 mg, 0.312 mmol) and the mixture allowed to stir overnight at room temperature. The volatiles were evaporated in vacuo, the residue diluted with ethyl acetate and subjected to preparative chromatography using a mixture of dichloromethane/methanol (9:1) as eluant. Material eluting with R_f= 0.72 was collected and the solvent evaporated in vacuo affording 40 mg (25 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.53 (s, 1H), 5.03 (dm, 1H), 4.12-4.04 (m, 2H), 4.01 (s, 2H), 3.79-3.71 (m, 2H), 2.88 (m, 2H), 1.62 (s, 9H), 1.59 (s, 9H).

MS: APCI (+): 513.3 (M+H).

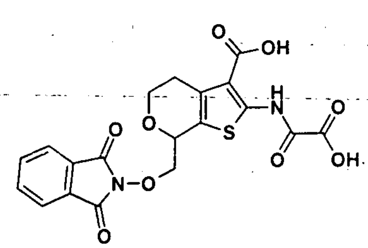
The above 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (40 mg) was dissolved in 50 % trifluoroacetic acid in dichloromethane (1 ml) and stirred at room temperature for 3 hours. The mixture was concentrated in vacuo, the residue titurated with dichloromethane and methanol which afforded after drying in vacuo 18 mg (87 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6 + CD_3OD) δ 4.98 (dm, 1H), 4.16 (s, 2H), 4.14-4.02 (m, 2H), 3.78-3.72 (m, 2H), 2.91 (m, 2H).

APCI (-): 399 (M-H);

LC-MS: s, 99%.

EXAMPLE 24



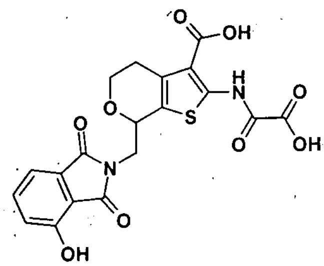
7-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.5 g, 1.2 mmol), 2-hydroxy-isoindole-1,3-dione (0.21 g, 1.3 mmol) and triphenylphosphine (0.35 g, 1.33 mmol) in dry tetrahydrofuran (20 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (205 μl, 1.33 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and the resultant solid dissolved in ethyl acetate (50 ml). The organic phase was washed with saturated aqueous sodium hydrogencarbonate (3 x 30 ml), water (3 x 50 ml), dried(Na_2SO_4), filtered and evaporated in vacuo. The residue (1.02 g) was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexane (1:2) as eluant. Pure fractions were collected affording after evaporation in vacuo 0.37 g (54 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

The above di-*tert*-butyl ester (0.33 g, 0.59 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (2 ml). The reaction was stirred at room temperature for 6.5 h. The volatiles were evaporated in vacuo and the residue trituated with a mixture of diethyl ether and heptane (5 ml, 1:1). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 200 mg (77 %) of the title compound as a solid.

M.p.: 251.5 - 254 °C;
Calculated for $C_{19}H_{14}N_2O_9S$;
C, 51.12 %; H, 3.16 %; N, 6.28 %. Found:
C, 51.46 %; H, 3.71 %; N, 5.87 %.

EXAMPLE 25



7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (0.5 g, 3.03 mmol) in anhydrous N,N-dimethylformamide (6 ml) under nitrogen was added diisopropylethylamine (1.05 ml, 6.06 mmol). The solution was stirred with cooling in an ice bath and chloromethyl methyl ether (0.46 ml, 6.06 mmol) was added. The reaction was allowed to slowly warm to ambient temperature and then stirred for an additional 7 h. The mixture was concentrated in vacuo to a small volume and diluted with ethyl acetate (75 ml). The organic layer was washed with water (2 x 40 ml), brine (20 ml), dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 0.6 g (95 %) of 4-methoxymethoxy-isobenzofuran-1,3-dione as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, J = 8, 1H), 7.62 (d, J = 8, 1H), 7.59 (d, J = 8, 1H), 5.43 (s, 2H), 3.55 (s, 3H).

A mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.15 g, 0.53 mmol) and 4-methoxymethoxy-isobenzofuran-1,3-dione (135 mg, 0.64 mmol) was dissolved in distilled acetonitrile (7 ml) under nitrogen. The flask was cooled in an ice bath with stirring and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.12 g, 0.64 mmol), and triethylamine (0.22 ml, 1.59 mmol) were added. The reaction was warmed to ambient temperature and stirred for 18 h. The solution was concentrated in vacuo

and the residue dissolved in ethyl acetate (40 ml). The organic layer was washed with 1% hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (10 ml), and brine (10 ml). The resulting solution was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo which afforded 0.18 g of a crude 2-amino-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.51 (d, J = 8 , 1H), 6.00-5.86 (2s, 2H), 5.39 (s, 2H), 4.94-4.89 (m, 1H), 4.18-4.02 (m, 2H), 3.86-3.65 (m, 2H), 3.54 (s, 3H), 2.85-2.73 (m, 2H), 1.55 (s, 9H).

APCI-MS: $[M+H]^+$ = 475.4

To a solution of crude 2-amino-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.18 g) in distilled dichloromethane (4 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.23 g, 1.2 mmol). The reaction was stirred for 3 hours., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The resulting solution was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 5 % gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 90 mg (28 % in two steps) of 2-(*tert*-butoxyoxalyl-amino)-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 7.64 (t, J = 8, 1H), 7.51 (d, J = 8, 1H), 7.46 (d, J = 8, 1H), 5.40 (s, 2H), 5.11-5.07 (m, 1H), 4.16-4.08 (m, 2H), 3.84-3.72 (m, 2H), 3.55 (s, 3H), 2.95-2.81 (m, 2H), 1.62 (s, 9H), 1.59 (s, 9H).

APCI-MS: $[M+H]^+$ = 603.8

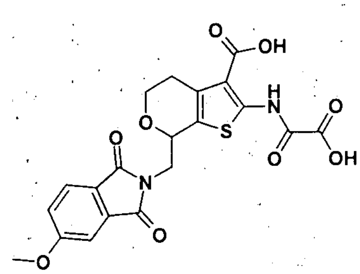
The above 2-(*tert*-butoxyoxalyl-amino)-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (86 mg, 0.143 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction was stirred at ambient temperature for 7 h., concentrated <u>in</u> <u>vacuo</u> and evaporated <u>in</u> <u>vacuo</u> from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried <u>in</u> <u>vacuo</u> to give 55 mg (86 %) of the <u>title</u> <u>compound</u> as a solid.

^{1}H NMR (400 MHz, d_6-DMSO) δ 12.34 (s, 1H), 11.10 (s, 1H), 7.63 (t, J = 8, 1H), 7.31 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 4.99-4.95 (m, 1H), 4.05-4.00 (m, 1H), 3.91-3.86 (m, 1H), 3.76-3.66 (m, 2H), 2.88-2.80 (m, 2H):

APCI-MS: $[M+H]^+$ = 447.4

HPLC (254.4nm): R_t=2.921 min, 100%

<u>EXAMPLE 26</u>

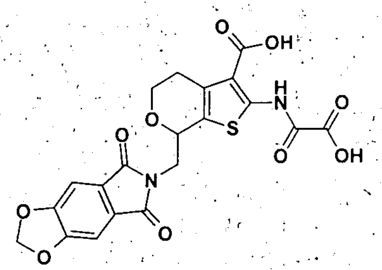


<u>7-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid</u>

The <u>title</u> <u>compound</u> was prepared in a similar way as described in Example 25.

M.p.: 234 - 236 °C;
Calculated for $C_{20}H_{16}N_2O_9S$, 0.25 x H_2O;
C, 51.67 %; H, 3.58 %; N, 6.03 %. Found:
C, 51.95 %; H, 3.92 %; N, 6.06 %.

EXAMPLE 27

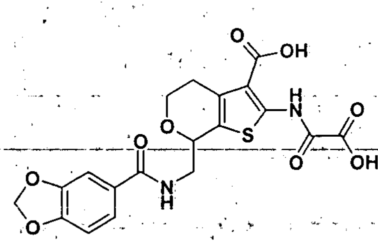


7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

M.p.: 239.5 - 242.5 °C;
Calculated for $C_{20}H_{14}N_2O_{10}S$, 0.1 x H_2O;
C, 50.45 %; H, 3.01 %; N, 5.88 %. Found:
C, 51.06 %; H, 3.43 %; N, 5.93 %.

EXAMPLE 28



7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Phthalimidoacetaldehyde diethyl acetal (100 g, 0.38 mol) and 1 N hydrochloric acid (600 ml) was mixture was stirred at reflux temperature for 5 min. or until a homogeneous solution is obtained. The reaction mixture was cooled and the precipitate was filtered off and dried in vacuo at 50 °C for 16 h which afforded 63.3 g (88 %) of phthalimido-acetaldehyde as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2H), 7.76 - 7.78(m, 2H), 7.90 - 7.92 (m, 2H), 9.67 (s, 1H).

To a mixture of phthalimidoacetaldehyde (64 g, 0.34 mol) and trans-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (81.5 g, 0.38 mol) in benzene (600 ml) stirred for 15 min. under nitrogen was added dropwise a 45 % solution of zinc chloride diethyl ether complex in dichloromethane (55.5 ml, 0.17 mol) at 0 °C. The reaction was allowed warm up to room temperature overnight. To the reaction mixture was added water (500 ml) and the resulting mixture was extracted with ethyl acetate (200 ml). The organic extract was washed successively with 1.0 N hydrochloric acid (2 x 200 ml) and brine (200 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated in vacuo which afforded a slowly crystallising oil (98 g). To the solid was added a mixture of ethyl acetate and diethyl ether (400 ml, 1:1) and the resulting precipitate was filtered off, washed with a small portion of diethyl ether and dried at 50 °C for 1h affording 59.8 g (69 %) of 2-(4-oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid. The filtrate was evaporated in vacuo and the residue purified by column chromatography on silica gel (1 L) using a mixture of ethyl acetate and heptane (1:2) as eluant. Pure fractions were collected and the solvent evaporated in vacuo to almost dryness, the solid was filtered off and dried in vacuo at 50 °C for 16 h affording an additional 15 g (17 %) of 2-(4-oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (d, 2H), 3.85 (dd, 1H), 4.18 (dd, 1H), 4.76 (m, 1H), 5.43 (d, 1H), 7.28 (d, 1H), 7.69 - 7.77 (m, 2H), 7.84 - 7.88 (m, 2H).

2-(4-Oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione (13 g, 0.051 mol) was dissolved in ethyl acetate (250 ml) and placed in a Parr bottle. 10 % Pd/C (1.5 g) was carefully added and the mixture was shaken under a pressure of 30 psi of hydrogen for 6.5 h (Parr apparatus). Filtration followed by evaporation of the ethyl acetate in vacuo afforded a crude 11.5 g of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione pure enough for the next step. Analytical pure compound could be obtained by purification of a small sample (250 mg) by column chromatography on silica gel, utilising a mixture of hexane/ethyl acetate as a gradient (from 100/0 to 50/50). Pure fractions were collected and the solvent evaporated in vacuo affording 142 mg (55 %) of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 - 2.68 (m, 4H), 3.62 (m, 1H), 3.74 (m, 1H), 4.00 (m, 2H), 7.75 (m, 2H), 7.88 (m, 2H).

To a mixture of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione (11.5 g, 44 mmol), *tert*-butyl cyanoacetate (6.9 g, 49 mmol) and elemental sulfur (1.6 g, 49 mmol) in ethanol (250 ml) was added morpholin (15 ml) and the resulting mixture was stirred at 50 °C for 16 h. The cooled reaction mixture was filtered and the precipitate filtered off and washed with diethyl ether and dried in vacuo affording 6.5 g (35 %) of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
The filtrate was evaporated in vacuo and the residue was dissolved in ethyl acetate (200 ml) washed with water (2 x 100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo affording 6.0 g (33 %) of almost regioisomer-pure 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.54 - 2.63 (m, 1H), 2.84 - 2.90 (m, 1H), 3.79 (q, 1H), 3.96 - 4.04 (m, 2H), 4.48 - 4.62 (m, 2H), 5.91 (bs, 2H, NH_2), 7.70 (m, 2H), 7.84 (m, 2H).

2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.71 - 2.90 (m, 2H), 3.67 - 3.77 (m, 2H), 4.02 - 4.15 (m, 2H), 4.90 (m, 1H), 6.04 (bs, 2H, NH_2), 7.70 (m, 2H), 7.84 (m, 2H).

To a solution of 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (6.0 g, 0.014 mol) in ethanol (100 ml) was added hydrazine-hydrate (1.4 ml, 0.029 mol). The mixture was stirred at reflux temperature for 1 h. The cooled reaction mixture was filtered and the solvent evaporated in vacuo. The residue was dissolved in diethyl ether (200 ml) and washed with water (100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo affording 2.9 g (71 %) of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

To a ice cooled mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1.4 g, 4.92 mmol), triethylamine (2 ml) in dichloromethane (100 ml) was added dropwise a solution of benzo[1,3]dioxole-5-carbonyl chloride (1.0 g, 5.41 mmol) in dichloromethane (25 ml) during 1.5 h. The ice cooled reaction mixture was stirred for an additional 0.5 h. The volatiles were evaporated in vacuo and the residue was dissolved in ethyl acetate (200 ml) and washed with water (2 x 100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (2 g) was subjected to flash column chromatography (1 l silicagel) using a mixture of ethyl acetate/hexane

(1:2) as eluant. Pure fractions were collected affording after evaporation in vacuo 0.3 g (14 %) of 2-amino-7-(((benzo[1,3]dioxole-5-carbonyl)amino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

TLC: R_f = 0.44 (ethyl acetate/heptane 1:1)

A mixture of the above 2-amino-7-(((benzo[1,3]dioxole-5-carbonyl)amino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 0.69 mmol), imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.16 g, 0.83 mmol) in dry tetrahydrofuran (50 ml) was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue was dissolved in ethyl acetate (100 ml) and washed with water (2 x 50 ml), brine (50 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (0.35 g) was subjected to flash column chromatography (500 ml silicagel) using a mixture of ethyl acetate/hexane (1:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo. The residue was trituated with diethyl ether (5 ml), filtered off and dried in vacuo at 50 °C for 5 h which afforded 0.17 g (44 %) of 7-(((benzo[1,3]dioxole-5-carbonyl)amino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

TLC: R_f = 0.37 (ethyl acetate/heptane 1.1).

The above di-*tert*-butyl ester (0.17 g, 0.30 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (20 ml). The reaction was stirred at room temperature for 5.5 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (10 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 72 h which afforded 100 mg (74 %) of the title compound as a solid.

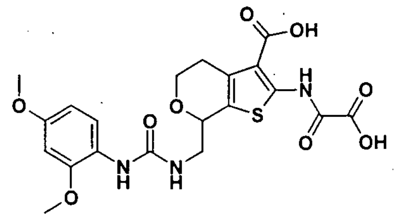
M.p.: 227 - 230° C;

Calculated for $C_{19}H_{16}N_2O_9S$, 0.5 x H_2O;

C, 49.89 %; H, 3.75 %; N, 6.12 %. Found:

C, 50.02 %; H, 3.68 %; N, 5.98 %.

EXAMPLE 29



7-[3-(2,4-Dimethoxy-phenyl)-ureidomethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (64 mg, 0.22 mmol) in dichloromethane (1 ml) was added 2,4-dimethoxyphenylisocyanate (40 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate (30 ml), washed with saturated sodium carbonate (3 x 25 ml), brine (3 x 25 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to preparative thin layer chromatography (100% dichloromethane). R_f=0.8 was isolated and the solvent evaporated in vacuo which afforded 55 mg (53 %) of 2-amino-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 9.6, 1H), 7.62 (d, J = 8.1, 1H), 6.45 (m, 3H), 5.00 (bs, 2H), 4.68 (m, 1H), 4.12 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.76-3.67 (m, 1H), 3.30 (dd, J = 14, 6.9, 1H), 2.76 (m, 2H), 1.55 (s, 9H).

MS: APCI (+): 464.3 (M+H).

To a solution of the above 2-amino-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (47 mg, 0.11 mmol) in dichloromethane (1 ml) was

added triethylamine (28 µl, 0.22 mmol) and midazol-1-yl-oxo-acetic acid *tert*-butyl ester (40 mg, 0.22 mmol). The mixture allowed to stir at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue diluted with ethyl acetate (35 ml). The organic phase was washed with saturated sodium carbonate (3 x 25 ml), brine (3 x 25 ml), dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography (60 % ethyl acetate/40 % hexanes). Pure 2-(*tert*-butoxyoxalyl-amino)-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester 34 mg (58 %) was isolated as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.70 (d, *J* = 9.6, 1H), 6.62 (bs, 1H), 6.47 (m, 3H), 5.02 (bs, 1H), 4.84 (m, 1H), 4.19 (dm, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75-3.70 (m, 1H), 3.36 (dd, *J* = 13.5, 7.5, 1H), 2.87 (m, 2H), 1.61 (s, 9H), 1.60 (s, 9H).

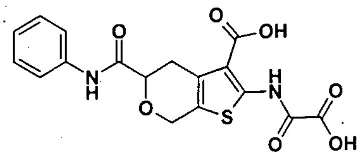
MS: APCI (+): 592.4 (M+H).

The above 2-(*tert*-butoxyoxalyl-amino)-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (34 mg) was dissolved in 20 % trifluoroacetic acid in dichloromethane (2 ml) and stirred at room temperature for 3 hours. The volatiles were evaporated in vacuo and the residue was titurated with diethyl ether (2x), filtered off and washed with a small amount of dichloromethane which afforded after drying in vacuo 16 mg (89 %) of the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (d, *J* = 9, 1H), 6.53 (d, *J* = 2.7, 1H), 6.44 (dd, *J* = 9, 2.7, 2H), 4.82 (m, 1H), 4.2 (m, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.67 (dd, *J* = 13, 4.5, 2H), 2.94 (m, 2H).

MS: APCI (+): 480.3 (M+H);

EXAMPLE 30



2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

A solution of glyoxylic acid ethyl ester, polymer form (2.02 g, 8.9 mmol) and (3-methoxy-1-methylene-allyloxy)-trimethyl-silane (1.9 ml, 8.9 mmol, Danishefsky's diene) in benzene (12 ml) was placed under nitrogen. Zinc chloride (0.5N in tetrahydrofuran, 8.9 ml, 4.45 mmol) was added and the reaction stirred at ambient temperature for 72 h. The mixture was concentrated in vacuo, diluted with ethyl acetate (100 ml) and washed with 1N hydrochloric acid (20 ml), saturated sodium bicarbonate (20 ml), and brine (20 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a mixture of ethyl acetate/hexane (1:2) as eluant. Pure fractions were collected and the solvent evaporated in vacuo which afforded 1.2 g (75 %) of 4-oxo-3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 6, 1H), 5.48 (d, J = 6, 1H), 5.01 (t, J = 8, 1H), 4.28 (q, J = 7, 2H), 2.85 (d, J = 8, 2H), 1.29 (t, J = 7, 3H).

To a solution of the above of 4-oxo-3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester (1.0 g, 5.9 mmol) in ethyl acetate (12 ml) was added 10 % palladium on activated carbon (0.15 g). The reaction was shaken on a Parr hydrogenator under a hydrogen atmosphere (30 psi) for 1.5 h. The mixture was filtered through celite and concentrated in vacuo. The residue was purified by silica gel chromatography using diethyl ether as eluant. Pure fractions were collected and the solvent evaporated in vacuo which affording 0.6 g (60 %) of 4-oxo-tetrahydro-2H-pyran-2-carboxylic acid ethyl as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 4.41-4.35 (m, 1H), 4.26 (q, *J* = 7, 2H), 3.81-3.70 (m, 1H), 2.73-2.58 (m, 3H), 2.44-2.36 (m, 1H), 1.29 (t, *J* = 7, 3H).

To a solution of 4-oxo-tetrahydro-2H-pyran-2-carboxylic acid ethyl (0.6 g, 3.5 mmol) in absolute ethanol (6 ml) was added sulfur (0.12 g, 3.85 mmol) and *tert*-butyl cyanoacetate (0.64 g, 4.55 mmol). The solution was stirred under nitrogen in a 50 °C oil bath and morpholin (0.61 ml, 7.0 mmol) was added. The reaction was stirred for 18 h. and then cooled to ambient temperature and excess sulfur removed by filtration. The filtrate was concentrated in vacuo and reconstituted in ethyl acetate (50 ml). The organic phase was washed with brine (2 x 10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (20 to 25 % gradient) as eluant. Pure fraction of the two isomers were collected and the solvent evaporated in vacuo which afforded 0.47 g of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester 5-ethyl ester (**A**) and 0.3 g of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (B) in 62 % combined yield.

(A)

^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (bs, 2H), 4.77-4.61 (m, 2H), 4.32-4.18 (m, 3H), 3.19-3.12 (m, 1H), 2.90-2.80 (m, 1H), 1.52 (s, 9H), 1.29 (t, *J* = 7, 3H).

APCI-MS: $[M+H]^+$ = 272.4 (loss of t-butyl)

(B)

^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.28-4.13 (m, 3H), 3.98-3.91 (m, 1H), 2.82-2.76 (m, 2H), 1.51 (s, 9H), 1.31 (t, *J* = 7, 3H).

APCI-MS: $[M+H]^+$ = 272.4 (loss of t-butyl)

The above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester 5-ethyl ester (275 mg, 0.84 mmol) was dissolved in a mixture of ethanol (4 ml) and tetrahydrofuran (1 ml). Sodium hydroxide

(1N, 1.6 ml, 1.68 mmol) was added and the reaction stirred at ambient temperature for 5 h. after which TLC analysis indicated that the reaction was complete. The reaction was monitored with a pH meter and neutralized with 1N hydrochloric acid until pH = 6.9. The solution was concentrated in vacuo to give 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester as a solid. Sodium chloride remained as an impurity.

^{1}H NMR (300 MHz, CD_3OD) δ 4.67-4.54 (m, 2H), 4.00-3.95 (m, 1H), 3.20-3.12 (m, 1H), 2.74-2.63 (m, 1H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 300.0

To a solution of the above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester (94 mg, 0.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (72 mg, 0.37 mmol) in distilled dichloromethane (4 ml) under nitrogen was added aniline (32 μl, 0.34 mmol) followed by 2,6-lutidine (0.11 ml, 0.93 mmol). The reaction was stirred for 72 h., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1% hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml), brine (10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 51 mg (45 %) of 2-amino-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.60 (d, 1H, J = 7), 7.49 (d, 1H, J = 8), 7.34 (t, 1H, J = 8), 7.32 (t, 1H, J = 8), 7.13 (t, 1H, J = 7), 6.03 (s, 2H), 4.82-4.73 (m, 2H), 4.25-4.22 (m, 1H), 3.43-3.38 (m, 1H), 2.79-2.72 (m, 1H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 375.5

To a solution of the above 2-amino-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (51 mg, 0.14 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (80 mg, 0.42 mmol) and triethylamine (38 μl, 0.28 mmol). The reaction was stirred for 4 h., concentrated in vacuo

and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 4 % mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 41 mg (26 % over two steps) of 2-(*tert*-butoxyoxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.40 (s, 1H), 7.59 (d, J = 8, 2H), 7.33 (t, J = 8, 2H), 7.12 (t, J = 7, 1H), 5.01-4.85 (m, 2H), 4.27-4.22 (m, 1H), 3.54-3.47 (m, 1H), 3.89-2.79 (m, 1H), 1.60 (s, 9H), 1.58 (s, 9H).

APCI-MS: $[M+H]^+$ = 503.2

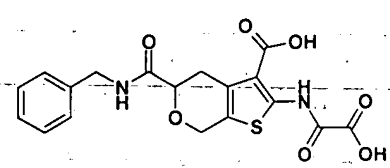
The above 2-(*tert*-butoxyoxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (37 mg, 0.074 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with ethyl ether and dried in vacuo to give 18 mg (62 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.85 (s, 1H), 7.69 (d, J = 8, 2H), 7.31 (t, J = 8, 2H), 7.07 (t, J = 7, 1H), 4.98 (d, J = 15, 1H), 4.83 (d, J = 15, 1H), 4.35-4.31 (m, 1H), 3.23 (d, J = 17, 1H), 2.84 (dd, J = 17, 10, 1H).

APCI-MS: $[M+H]^+$ = 391.3

HPLC (254.4nm): R_t=3.22 min, 100%

EXAMPLE 31



5-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester (101 mg, 0.34 mmol, prepared in Example 31) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (78 mg, 0.41 mmol) in distilled dichloromethane (4 ml) under nitrogen was added benzylamine (40 μl, 0.37 mmol) followed by 2,6-lutidine (0.12 ml, 1.02 mmol). The reaction was stirred for 72 h., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1 % hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml), brine (10 ml), dried (Na_2SO_4) over sodium sulfate, filtered, and the solvent evaporated in vacuo to give 72 mg (56 %) of 2-amino-5-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.66 (s, 2H), 4.44 (d, J = 5, 2H), 4.17-4.13 (m, 1H), 3.40-3.33 (m, 1H), 2.75-2.66 (m, 1H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 389.5

To a solution of the above 2-amino-5-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester (72 mg, 0.19 mmol) in distilled dichloromethane (4 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.57 mmol) and triethylamine (51 μl, 0.38 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (5 to 10 % gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo to give 42 mg (24 % over two steps) of 5-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-

amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 7.37-7.29 (m, 5H), 6.97 (t, 1H, J = 6), 4.89-4.77 (m, 2H), 4.58-4.46 (m, 2H), 4.20-4.16 (m, 1H), 3.50-3.44 (m, 1H), 2.84-2.76 (m, 1H), 1.61 (s, 9H), 1.60 (s, 9H).

APCI-MS: $[M+H]^+$ = 517.3

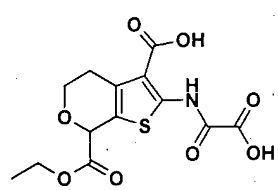
The above 5-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester (36 mg, 0.07 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction was stirred at ambient temperature for 7 h., concentrated <u>in vacuo</u> and evaporated <u>in vacuo</u> from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried <u>in vacuo</u> to give 14 mg (50 %) of the <u>title compound</u> as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.48 (t, J = 6, 1H), 7.31-7.20 (m, 5H), 4.91 (d, J = 15, 1H), 4.76 (d, J = 15, 1H), 4.32-4.29 (m, 2H), 4.20-4.16 (m, 1H), 3.22 (m, 1H, partially obscured by water), 2.70-2.63 (m, 1H).

APCI-MS: $[M+H]^+$ = 405.2

HPLC (254.4nm): R_t=3.06 min, 100 %

<u>EXAMPLE 32</u>



<u>2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester</u>

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (60 mg, 0.18 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.54 mmol) and triethylamine (50 µl, 0.36 mmol). The reaction was stirred for 4 h., concentrated <u>in vacuo</u>

and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 6 % mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 78 mg (95 %) of 2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.54 (s, 1H), 5.28 (s, 1H), 4.27 (q, 2H, J = 7), 4.25-4.18 (m, 1H), 4.04-3.96 (m, 1H), 2.96-2.80 (m, 2H), 1.60 (s, 9H), 1.57 (s, 9H).

LC-MS: R_t=3.97 min, $[M+H]^+$ = 456.3

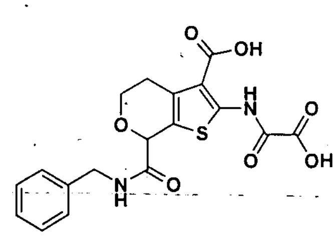
The above 2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (72 mg, 0.16 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 48 mg (88 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 5.47 (s, 1H), 4.19 (q, J = 7, 2H), 3.98-3.94 (m, 2H), 2.90-2.78 (m, 2H), 1.23 (t, J = 7, 3H).

APCI-MS: $[M+H]^+$ = 344.2

HPLC (254.4nm): R_t=2.82 min, 100 %

EXAMPLE 33



7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (0.12 g, 0.37 mmol) in ethanol (3 ml) was added potassium hydroxide (56 mg, 1.0 mmol) dissolved in a minimum amount of water. The mixture was stirred for 24 h., then 1N hydrochloric acid was added until pH = 7. The solution was concentrated in vacuo and the residue partitioned between ethyl acetate (35 ml) and water (10 ml). The layers were separated and 1 % hydrochloric acid (1 ml) was added to the aqueous layer. The aqueous layer was then extracted further with ethyl acetate (3 x 15 ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and filtered. Triethylamine (3 drops) was added to the solution to stabilize the acid-sensitive compound. The solution was concentrated in vacuo affording 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester triethylamine salt (approximately 0.13 g) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.28-4.23 (m, 1H), 3.90-3.85 (m, 1H), 2.88-2.71 (m, 3H), 1.56 (s, 9H).

A solution of the above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester triethylamine salt (0.12 g, 0.30 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (71 mg, 0.36 mmol) was prepared in distilled acetonitrile under nitrogen. Benzylamine (36 μl, 0.33 mmol) was added followed by 2,6-lutidine (70 μl, 0.60 mmol). The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 5 ml), and brine (10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo which afforded crude 2-amino-7-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester which was used without purification.

To a solution of the above crude 2-amino-7-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (77 mg, 0.2 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.6 mmol) and triethylamine (55 μl,

0.4 mmol). The reaction was stirred for 5 h., concentrated in vacuo and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 29 mg (19 % over two steps) of 7-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.35-7.26 (m, 5H), 6.96 (t, J = 6, 1H), 5.20 (s, 1H), 4.55-4.41 (m, 2H), 4.22-4.17 (m, 1H), 3.87-3.81 (m, 1H), 2.97-2.84 (m, 2H), 1.61 (s, 9H), 1.59 (s, 9H).

APCI-MS: $[M-H]^-$ = 516

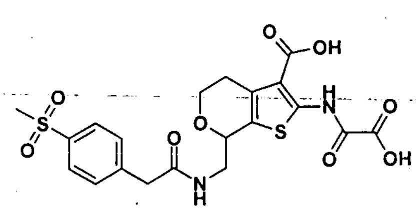
The above 7-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (29 mg, 0.06 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 18 mg (80 %) of the title compound as an solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.67 (t, J = 6, 1H), 7.30-7.21 (m, 5H), 5.23 (s, 1H), 4.31-4.28 (m, 2H), 4.13-4.10 (m, 1H), 3.88-3.85 (m, 1H), 2.86 (bs, 2H).

APCI-MS: $[M+H]^+$ = 405

HPLC (254.4nm): R_t=3.12 min, 94 %

EXAMPLE 34



7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of (4-methanesulfonyl-phenyl)-acetic acid (90.4 mg, 0.42 mmol) in a mixture of dichloromethane (3 ml) and N,N-dimethylformamide (1 ml) cooled at 0 °C was added diisopropyl-ethylamine (306 μl, 1.76 mmol), diisopropylazodicarboxylate (72 μl, 0.45 mmol) and 1-hydroxy-benzotriazole (56.6 mg, 0.42 mmol). After being stirred for 20 minutes, 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (100 mg, 0.35 mmol) dissolved in dichloromethane (1 ml) was added via syringe. The reaction mixture was stirred for 18 h. while slowly warming to room temperature. The volatiles were evaporated in vacuo and the residue diluted with ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (3 x 50 ml), 1 % hydrochloric acid (3 x 50 ml), brine (3 x 50 ml),dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9) as eluant. Fraction with R_f=0.5 was isolated which afforded after evaporating the solvent in vacuo 115 mg (69 %) of 2-amino-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7, 2H), 7.39 (d, J = 7.5, 2H), 5.91 (bs, 2H), 4.65 (m, 1H), 4.09 (dt, J = 7.8, 3.3, 1H), 3.85-3.65 (m, 2H), 3.61 (s, 2H), 3.45-3.38 (m, 2H), 3.05 (s, 3H), 2.75 (m, 2H), 1.56 (s, 9H).

MS: APCI (+): 481 (M+H).

To a solution of the above 2-amino-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (110 mg, 0.23 mmol) in dichloromethane (3 ml) was added triethylamine (96 μl, 0.69 mmol) and midazol-1-yl-oxo-acetic acid *tert*-butyl ester (134 mg, 0.69 mmol).

The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, diluted in ethyl acetate (50 ml), washed with saturated sodium carbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9). Fraction with R_f=0.5 was collected and the solvent evaporated in vacuo affording 70 mg (50 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.88 (d, *J* = 8.1, 2H), 7.46 (d, *J* = 8.1, 2H), 5.88 (bs, 1H), 4.78 (m, 1H), 4.15 (dt, *J* = 12, 4, 1H), 3.86-3.71 (m, 2H), 3.64 (s, 2H), 3.42-3.34 (m, 2H), 3.04 (s, 3H), 2.85 (m, 2H), 1.62 (s, 9H), 1.61 (s, 9H).

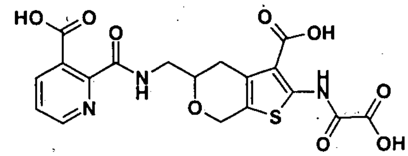
MS: APCI (+): 609 (M+H)[minor], 497 (-2 *tert* butyls)[major];
LC-MS: s, 99 %

The above 2-(*tert*-butoxyoxalyl-amino)-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (60 mg, 0.098 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (2 ml) and allowed to stir at room temperature for 3 hours. The reaction mixture was concentrated in vacuo, the residue titurated with diethyl ether (3x), and dried in vacuo which afforded 45 mg (92 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.47 (m, 1H), 7.82 (d, *J* = 7.8, 2H), 7.50 (d, *J* = 7.8, 2H), 4.75 (bs, 1H), 4.10 (m, 1H), 3.69 (m, 1H), 3.60 (d, *J* = 3.6, 2H), 3.52 (m, 1H), 3.35 (m, 2H), 3.18 (s, 3H), 2.83 (m, 2H).

MS: APCI (-): 495 (M-H); LC-MS: s, 95 %.

EXAMPLE 35



2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid

2-(*tert*-Butoxyoxalyl-amino)-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (164 mg, 0.58 mmol) was stirred for 20 h at 80 °C with furo[3,4-b]pyridine-5,7-dione (86.1 mg, 0.58 mmol) in a mixture of tetrahydrofuran (1.0 ml) and N,N-dimethylformamide (0.25 ml). The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate (50 ml) and washed with water (3 x 30ml). The organic layer was dried($MgSO_4$), filtered, and the solvent evaporated in vacuo. The residue (78 mg) was purified by preparative TLC (hexane/ethyl acetate, 50:50) which afforded 2 products: 2-((2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid **(A)** (27.9 mg, 11 %) and 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**B**) (21.3 mg, 9 %).

(A)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.74 (d, J = 3.3, 1H), 8.14 (d, J =7.5, 1H), 7.40 (dd, J = 4.8, J = 5.1, 1H), 6.71 (m, 1H), 5.98 (s, 2H), 4.63 (s, 2H), 4.00 (m, 1H), 3.42 (m, 1H), 2.90 (dd, J = 3.3, J = 3.6, 1H), 2.59 (dd, J = 11, J = 11, 1H), 1.48 (s, 9H).

MS *m/z* 434 (M+);

(B)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 5.1, 1H), 8.20 (d, J = 9, 1H), 7.64 (dd, J = 5.7, 4.8, 1H), 5.94 (s, 2H), 4.60 (d, J = 14, 1H), 4.51 (d, J = 14, 1H), 4.05 (m, 2H), 3.87 (d, J = 12.5, 1H), 2.92 (d, J = 17, 1H), 2.61 (m, 1H), 1.53 (s, 9H).

MS: APCI (+): 416 (M+1)[minor], 360 (M- *tert*-butyl) [major].

To a solution of the above 2-((2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid (27.9 mg, 0.064 mmol) in tetrahydrofuran (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (38 mg, 0.193 mmol) and triethylamine (9 μl, 0.064 mmol). The resulting mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (20 ml) and washed with water (3 x 10 ml). The extracts were dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by preparative TLC (0.5mm, hexane/ethyl acetate, 1/1 to 2/3 gradient). After evaporation of the solvent in vacuo 917 mg (46 %) of 2-(3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid was isolated as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.75 (s, 1H), 8.15 (d, *J* = 7.5, 1H), 7.42 (dd, *J* = 6.9, *J* = 5.1, 1H), 6.73 (m, 1H), 4.81 (dd, *J* = 15.3, *J* = 14.4, 2H), 4.03 (m, 1H), 3.83 (m, 1H), 3.47 (m, 1H), 2.99 (d, *J* = 17.1, 1H), 2.59 (dd, *J* = 11.1, *J* = 10.8, 1H), 1.61 (s, 9H), 1.48 (s, 9H).

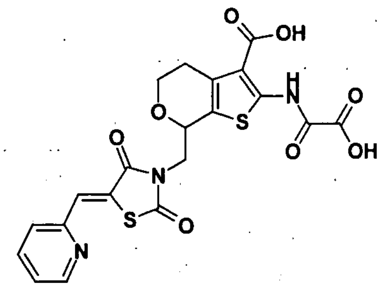
MS: 506 (M-55).

The above 2-(3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid (13.1 mg, 0.023 mmol) was stirred in 50 % trifluoroacetic acid in dichloromethane (2 ml) at room temperature for 7 h. The solvent was evaporated in vacuo which afforded 10 mg (96%) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.77 (d, *J* = 7.7, 1H), 8.16 (d, *J* = 7.5, 1H), 7.60 (d, *J* = 7.8, 1H), 4.88 (d, *J* = 9, 1H), 4.76 (d, *J* = 9, 1H), 3.96 (m, 1H), 3.02 (m, 1H), 2.78 (m, 1H).

MS: 481 (M+33).

EXAMPLE 36



7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

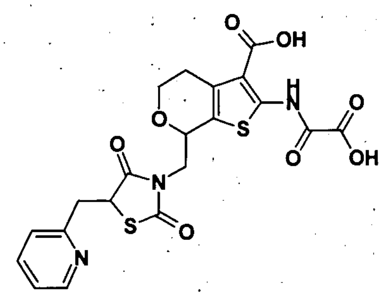
To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1.0 g, 2.42 mmol), 5-pyridin-2-ylmethylene-thiazolidine-2,4-dione (0.55 g, 2.66 mmol, prepared in a similar way as described in J. *Med. Chem.* **41** (10), 1619-1630 (1998)) and triphenylphosphine (0.7 g, 2.66 mmol) in dry tetrahydrofuran (75 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (420 µl ml, 2.66 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo, the resultant solid was washed with diethyl ether, filtered off and dried in vacuo at 50 °C for h affording 1.4 g (96 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

TLC: R_f = 0.46 (ethyl acetate/heptane 1:1).

The above di-*tert*-butyl ester (1.0 g, 1.66 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (30 ml). The reaction was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (50 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 16 h which afforded 0.8 g of semi pure title compound. The title compound (0.8 g) was suspended in ethyl acetate (25 ml) and heated at reflux temperature for 0.5 h. Isopropanol (5 ml) was added and the mixture was cooled to room temperature the precipitate filtered off and dried in vacuo at 50 °C for 16 h which afforded 0.37 g (37 %) of the title compound as a solid.

Calculated for $C_{20}H_{15}N_3O_8S_2$, 0.5 x H_2O, 0.75 x isopropanol;
C, 49.17 %; H, 4.08 %; N, 7.73 %. Found:
C, 48.97 %; H, 4.03 %; N, 7.45 %.

EXAMPLE 37



7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

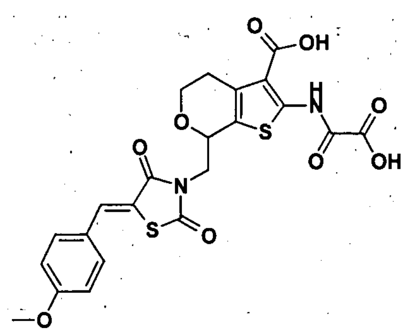
To a solution of 5-pyridin-2-ylmethylene-thiazolidine-2,4-dione (5.0 g, 0.024 mol, prepared in a similar way as described in J. *Med. Chem.* **41** (10), 1619-1630 (1998)) in tetrahydrofuran (300 ml) was added 10 % palladium on carbon (1 g) and the resulting mixture was hydrogenated. After 50 ml of hydrogen was consumed and additional portion of 10 % palladium on carbon (5 g) was added and the hydrogenation was continued at 50 psi for 16 h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was subjected to flash column chromatography (1 l silicagel) using a mixture of ethyl acetate/hexane (1:1) as eluant. Semi pure fractions were collected and the solvent evaporated in vacuo affording 0.8 g (16 %) of 5-pyridin-2-ylmethyl-thiazolidine-2,4-dione as a solid.

To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.7 g, 1.69 mmol), 5-pyridin-2-ylmethyl-thiazolidine-2,4-dione (0.36 g, 1.86 mmol) and triphenylphosphine (0.49 g, 1.86 mmol) in dry tetrahydrofuran (40 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (290 µl ml, 1.86 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo, the resultant residue was subjected to

flash column chromatography (0.5 l silicagel) using a mixture of ethyl acetate/hexane (1:2) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.6 g (59 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
TLC: R_f = 0.43 (ethyl acetate/heptane 1:1).
The above di-*tert*-butyl ester (0.5 g, 0.83 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue triturated with diethyl ether (20 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 1 h which afforded 0.3 g of semi pure title compound. The title compound (0.3 g) was suspended in isopropanol (15 ml) and heated at reflux temperature for 5 min., cooled to room temperature and the precipitate filtered off and dried in vacuo at 50 °C for 16 h which afforded 0.2 g (49 %) of the title compound as a solid.

M.p.: > 250 °C;
Calculated for $C_{20}H_{17}N_3O_8S_2$, 0.25 x H_2O;
C, 48.43 %; H, 3.56 %; N, 8.47 %. Found:
C, 48.41 %; H, 3.57 %; N, 8.10 %.

EXAMPLE 38



7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

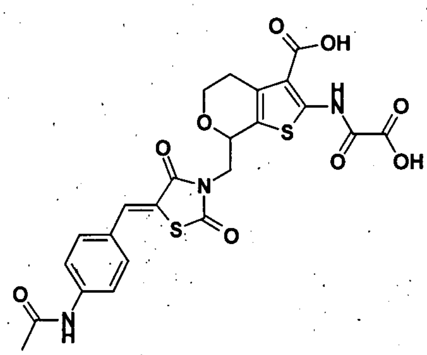
M.p.: 236 - 238 °C;

Calculated for $C_{22}H_{18}N_3O_9S_2$, 0.5 x H_2O;

C, 50.09 %; H, 3.63 %; N, 5.31 %. Found:

C, 49.92 %; H, 3.59 %; N, 5.18 %.

EXAMPLE 39



7-[5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

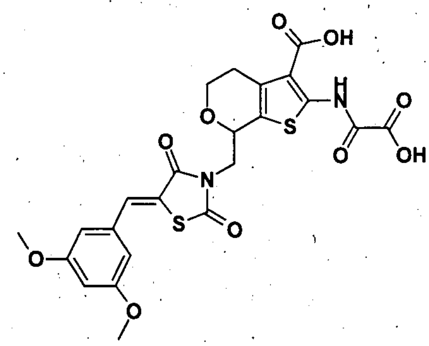
M.p.: > 250 °C;

Calculated for $C_{23}H_{19}N_3O_9S_2$, 2 x H_2O;

C, 47.50 %; H, 3.99 %; N, 7.23 %. Found:

C, 47.60 %; H, 3.45 %; N, 6.80 %.

EXAMPLE 40



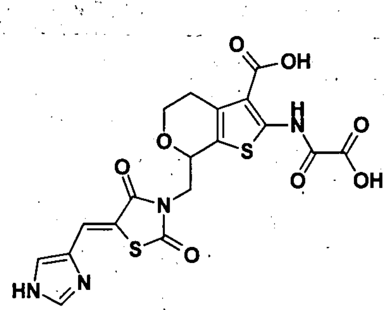
7-[5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.92 (s, 1H), 6.80 (d, J = 1.8, 2H), 6.66 (t, J = 2.1, 1H), 5.00 (m, 1H), 4.06 (bm, 2H), 3.81 (s, 6H), 3.71 (dd, J = 6.6, 6, 2H), 2.83 (m, 2H).

MS: APCI (+): 549 (M+H); LC-MS; s, 90 %.

EXAMPLE 41



7-[5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

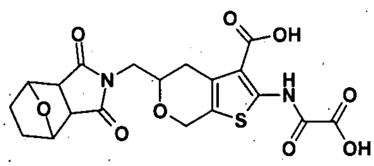
M.p.: > 250 °C;

Calculated for $C_{18}H_{14}N_4O_8S_2$;

C, 40.65 %; H, 2.56 %; N, 9.17 %. Found:

C, 40.54 %; H, 2.55 %; N, 9.46 %.

EXAMPLE 42



5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.20 g, 0.48 mmol) in tetrahydrofuran (5 ml) was added 10-oxa-4-aza-tricyclo(5,2,1,0,2,6)decane-3,5-dione (81 mg, 0.48 mmol) and triphenylphosphine (126 mg, 0.48 mmol). The mixture was cooled to 0 °C and diisopropylazodicarboxylate (94.5 μl, 0.48 mmol) was added via syringe. The reaction was stirred for 18h. while slowly warming to room temperature. The volatiles were evaporated in vacuo, and the residue diluted into ethyl acetate (50 ml), washed with saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The semi-solid residue was subjected to preparative thin layer chromatography using a mixture of ethyl acetate/hexanes (4:1) as eluant. Fraction with R_f=0.68 was isolated which afforded 64 mg (24 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 4.89 (m, 2H), 4.80-4.61 (m, 2H), 3.93-3.86 (m, 1H), 3.83-3.79 (m, 1H), 3.62-3.57 (dd, *J* = 12.6, 3.6, 1H), 2.92 (q, 6.9, 2H), 2.60 (dd, *J* =17.1, 10.5, 2H), 1.85 (m, 2H), 1.60 (s, 18H).

MS: APCI (-): 561 (M-H).

The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (51 mg) was dissolved in

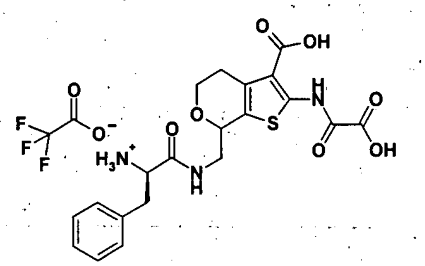
50% trifluoroacetic acid in dichloromethane (5ml) and stirred at room temperature for 2 h. The reaction mixture was evaporated in vacuo and the residue titurated with diethyl ether (3 x 10 ml). The solid was filtered of and dried affording 30 mg (71 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 7.68 (bs, 1H), 4.69 (s, 2H), 4.67 (d, J = 15, 1H), 4.56 (d, J = 15, 1H), 3.63 (bm, 1H), 3.50 (d, J = 5, 1H), 3.46 (d, J = 5, 1H), 3.08 (d, J = 15, 2H), 2.94 (d, J = 2.4, 1H), 2.89 (m, 1H), 1.64 (s, 4H).

MS: APCI (-): 449 (M-H);

LC-MS: s, 95 %

EXAMPLE 43



7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid, trifluoroacetic acid salt.

To a stirred solution of a mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.7 g, 16 mmol) was added diisopropylethylamine (2.8 ml, 16 mmol) and succinimidyl-2,2,2-trichloroethylcarbonate (4.8 g , 16 mmol) portion wise. The reaction mixture was stirred at room temperature for 18 h, washed with saturated sodium hydrogen carbonate, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographyed on silica (90 g) using a mixture of ethyl acetate/heptane (1:1) as eluant. Pure fraction were collected and the solvent evaporated in vacuo affording 6.78 g of crude product which was

dissolved in dichloromethane (5 ml) followed by heptane (30 ml) which was added as a top layer. After crystallisation and filtration 5.44 g (74 %) of 2-amino-7-((2,2,2-trichloro-ethoxycarbonyl-amino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained as an oil.

^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.78 (m, 2H), 3.32 (m, 1H), 3.62 (m,1H), 3.72 (m,1H), 4.15 (m, 1H), 4,68 (m, 1H), 4.71 (s, 2H), 6.00 (s, 2H).

The above 2-amino-7-((2,2,2-trichloro-ethoxycarbonylamino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.0 g, 8.0 mmol) was dissolved in a mixture of tetrahydrofuran (15 ml) and a aqueous phosphate buffer (pH 3; 5 ml) followed by addition of zinc (16 g, 0.244 mol). The reaction mixture was stirred for 6 h at room temperature at which time the solvent was removed in vacuo. To the residue was added diethyl ether (20 ml) and water (40 ml). Sodium carbonate was added to the aqueous phase until pH = 8 and the aqueous phase was extracted with dichloromethane (3x). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (90 g) using a mixture of dichloromethane/ethanol/25 % ammonia in water 100:10:0.7 as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 1.52 g (61 %) of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.69 (dt, 2H).

Calculated for $C_{13}H_{20}N_3O_3S$;

C, 54.91 %; H, 7.09 %; N, 9.85 %. Found:

C, 54.53 %; H, 7.19 %; N, 9.61 %.

LC-MS : Mw = 285,2 R_t= 4.14 min

To a solution of boc-D-phe-OH (0.28 g, 1.05 mmol) in dichloromethane (10 ml) was added 1-hydroxy benzotriazole (0.14 g, 1.05 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.18 g, 1.054 mmol). The reaction mixture was stirred for 15 min at room temperature. 2-Amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.30 g, 1.054 mmol) dissolved in dichloromethane (15

ml) was added. Ethyl diisopropylamine (0.18 ml, 1.05 mmol) was added and the reaction mixture was stirred over night at room temperature. The reaction was washed with 10 % aqueous citric acid (15 ml), saturated aqueous sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent removed in vacuo affording 594 mg (100 %) of 2-amino-7-(((1R)-2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^1H NMR($CDCl_3$) δ 1.42 (s, 9H), 1.55 (s, 9H), 2.73 (m, 2H), 3.05 (m, 2H), 3.16 (m, 1H), 4.06 (m, 1H), 4.32 (m,1H), 5.05 (s, 1H), 6.01 (s, 2H), 6.10 (s, 1H), 7.20 (m, 5H).

LC-MS : Mw = 532.2, R_t = 7.11.

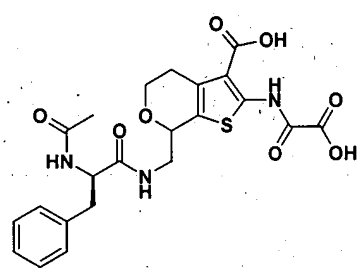
2-Amino-7-(((1R)-2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.58 g, 1.09 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.3 ml, 2.18 mmol) was added and the reaction mixture was cooled with in a ice bath. Imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.43 g, 2.18 mmol) dissolved in dichloromethane (5 ml) was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature diluted with dichloromethane (20 ml), washed with 1 N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate (15 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography silica gel (40 g) using a mixture of ethyl acetate/heptane 1:1 as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 512 mg (69 %) of 7-((1R)-(2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)methyl)-2-(*tert*-butoxyoxalylamino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.59 (s, 9H), 1.61 (s, 9H), 2.86 (m, 2H), 3.02 (m, 2H), 3.15 (m, 1H), 3.64 (m, 1H), 3.87 (m, 1H), 4.09 (m, 1H), 4.28 (m, 1H), 4.51 (m, 1H), 4.67 (m,1H), 5.10 (s, 1H), 6.00 (s, 1H), 7.20 (m, 5H), 12.5 (s, 1H).

7-((1R)-(2-*tert*-Butoxycarbonylamino-3-phenyl-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyrran-3-carboxylic acid *tert*-butyl ester (0.51 g, 0.76 mmol) was dissolved in dichloromethane (5 ml). Trifluoroacetic acid (5 ml) was added and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo (stripped 3 times with dichloromethane) which afforded 314 mg (92 %) of the title compound.

Calculated for $C_{20}H_{21}N_3O_7S$; 1 x CF_3COOH, 1 x H_2O;
C, 45.60 %; H, 4.17 %; N, 7.25 %. Found:
C, 45.78 %; H, 4.20 %; N, 7.05 %.
LC-MS : RT=3.61 / RT=3.77 Mw = 448.2

EXAMPLE 44



7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of Ac-D-Tyr-OH (235 mg, 1.05 mmol) dissolved in dichloromethane (10 ml) was added 1-hydroxybenzotriazole (0.14 g, 1.05 mmol), 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (0.20g , 1.05 mmol) and the reaction mixture was stirred for 15 min at room temperature. 2-Amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 1.05 mmol) dissolved in dichloromethane (10 ml) was added followed by N,N-diisopropyl-ethylamine (0.18 ml, 1.05 mmol). The resulting reaction mixture was stirred for 18 h at room temperature, diluted with dichloromethane (15 ml) was washed with 10 % aqueous citric acid (25 ml), saturated sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent removed in

vacuo. The residue was purified by flash chromatography on silica gel (40 g) using ethyl acetate as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 304 mg (59 %) of 7-((2-acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR ($CDCl_3$) double set of peaks from diastereomers; selected peaks: δ 1.55 (s, 9H), 1.95 (s, 3H), 2.74 (m, 2H), 2.92 (m, 2H), 3.23 (m, 1H), 3.63 (m, 2H), 6.05 (s, 2H).

LC-MS: R_t = 5.17, Mw = 490.4

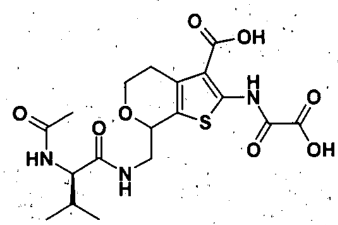
7-((2-Acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 0.61 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.17 ml, 1.22 mmol) was added and the reaction mixture was cooled to 0° C. Imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.24, 1.22 mmol) dissolved in dichloromethane (10 ml) was added dropwise. The resulting reaction mixture was stirred at room temperature for 18 h. Dichloromethane (20 ml) was added and the mixture was washed with 1 N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate (20 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (40 g) using ethyl acetate as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 208 mg (55 %) of 7-((2-acetylamino-3-(4-hydroxy-phenyl)-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS : Mw = 618.4, R_t = 6.97

7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.2 g, 0.32 mmol) was dissolved in dichloromethane (8 ml) and trifluoroacetic acid (4 ml) was added. The reaction mixture was stirred 7 h at room temperature. The solvent was evaporated in vacuo (stripped 3 times with dichloromethane) which afforded 200 mg (100 %) of the title compound.

Calculated for $C_{22}H_{23}N_3O_9S$, 3 x H_2O;
C, 47.22 %; H, 5.22 %; N, 7.51 %. Found:
C, 47.05 %; H, 4.88 %; N, 7.39 %.
LC-MS : R_t = 3.64, Mw = 506.4.

EXAMPLE 45



7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid.

To a solution of Ac-D-Val-OH (0.17 g, 1.09 mmol) dissolved in dichloromethane (15 ml) was added N,N-dimethylformamide (1 ml), 1-hydroxybenzotriazole (0.15 g, 1.09 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (0.21 g, 1.09 mmol). The reaction mixture was stirred for 15 min. at room temperature at which time a solution of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.31 g, 1.09 mmol) in dichloromethane (10 ml) was added followed by N-N-diisopropylethylamine (0.186 ml, 1.09 mmol). The resulting mixture was stirred over night at room temperature diluted with dichloromethane (10 ml) washed with 10 % aqueous citric acid (20 ml), sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo affording 415 mg (90 %) of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 0.98 (t, 2H), 1.55 (s, 9H), 2.02 (d, 1H), 2.77 m, (2H), 3.40 (m, 1H), 4.14 (m, 1H).

LC-MS : R_t = 5.17 Mw= 426.4

To a mixture of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.4 g,

0.94 mmol) dissolved in dichloromethane (10 ml) and triethylamine (0.26 g, 1.87 mmol) cooled to 0° C was added a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.37 g, 1.87 mmol) in dichloromethane (10 ml). The resulting mixture was stirred for 18 h at room temperature diluted with dichloromethane (20 ml) washed with 1N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo which afforded 515 mg (97 %) of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS: R_t = 7.11, Mw = 554.4.

HPLC: R_t = 34.16, Area (%) = 100 %.

To a solution of the above 7-((2-acetylamino-3-methyl-butyrylamino)-methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.5 g, 0.90 mmol) dissolved in dichloromethane (3 ml) was added trifluoroacetic acid (1 ml) and the reaction mixture was stirred for 18 h at room temperature. Trifluoroacetic acid (4 ml) was added and the mixture was stirred for an additional 3 hours at room temperature. The volatiles were evaporated in vacuo (and stripped 3 times with dichloromethane) affording 282 mg (71 %) of the title compound.

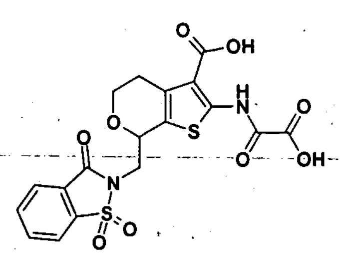
Calculated for $C_{18}H_{23}N_3O_8S$, 2 x H_2O;

C, 45.28 %; H, 5.70 %; N, 8.80 %. Found:

C, 45.20 %; H, 5.50 %; N, 8.80 %.

LC-MS: R_t = 3.60, Mw = 442.2

EXAMPLE 46



2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

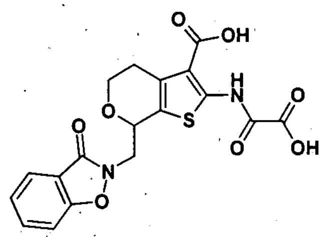
M.p.: 210 - 212 °C;

Calculated for $C_{18}H_{14}N_2O_9S_2$, 0.5 x H_2O, 0.75 x Ethyl acetate;

C, 44.49 %; H, 3.83 %; N, 5.32 %. Found:

C, 44.70 %; H, 3.61 %; N, 4.90 %.

EXAMPLE 47



2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

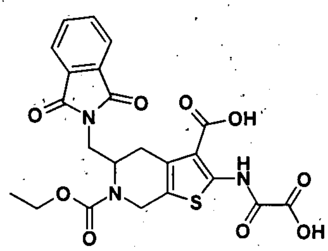
M.p.: 236 - 237 °C;

Calculated for $C_{18}H_{14}N_2O_8S$, 0.3 x H_2O;

C, 51.02 %; H, 3.47 %; N, 6.61 %. Found:

C, 51.16 %; H, 3.47 %; N, 6.31 %.

EXAMPLE 48



5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester

To a solution of 1,4-dioxa-8-aza-spiro[4,5]decane (51.5 g, 0.36 moles) in a mixture of dichloromethane (500 ml) and saturated sodium bicarbonate (500 ml) was added di-*tert*-butyldicarbonate (69.8 g, 0.32 moles) and the reaction was vigorously stirred for 3 hours. and the layers separated. The organic layer was washed with 1N hydrochloric acid (2 x 150 ml), brine (100 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo affording 75.5 g (97 %) of 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester as a crystallizing oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 4H), 3.49 (bm, 4H), 1.65 (bm, 4H), 1.45 (s, 9H).

To the above 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (4.0 g, 16.4 mmol) dissolved in dry diethyl ether (32 ml) was added 2,2' bipyridyl (1 mg) and the solution was cooled to –75 °C. Tetramethylethylenediamine (3.2 ml, 21.4 mmol) was added followed by dropwise addition of sec-butyl lithium (16.4 ml, 21.4 mmol, 1.3M in cyclohexane). The mixture was stirred at -75 °C for 10 min, then slowly warmed to -20 °C and stirred at that temperature for 0.5 h, then cooled to -30 °C. At this temperature, formaldehyde was generated by heating paraformaldehyde at 150 °C and passed through the mixture with dry nitrogen until the color faded to off-white, at which time water (40 ml) was added. The layers were separated, and the aqueous layer was washed diethyl ether (2 x 50 ml). The combined organic extracts were washed 1N hydrochloric acid (2 x 75 ml), saturated sodium bicarbonate solution (50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue (2.9 g) was purified by silica gel chromatography (hexane/ethyl acetate, 10 % ethyl acetate to 30 % ethyl acetate, gradient). Pure fractions were collected and the solvent evaporated in vacuo affording 1.3 g (29 %) of 7-hydroxy-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester as a thick oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (bm, 1H), 4.08-3.96 (m, 5H), 3.96-3.88 (m, 1H), 3.78-3.70 (m, 1H), 3.30-3.16 (bm, 1H), 2.30-1.98 (bs, 1H), 1.96-1.78 (m, 2H), 1.74-1.64 (m, 2H), 1.49 (s, 9H).

To 7-hydroxy-methyl-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (0.4 g, 1.5 mmol) dissolved in dry tetrahydrofuran (20 ml)

was added phthalimide (0.28 g, 1.9 mmol), triphenylphosphine (0.5 g, 1.9 mmol) and the mixture was cooled to 0 °C in an ice bath. Diethylazodicarboxylate (0.29 ml, 1.82 mmol) was added dropwise and the mixture was stirred at 0 °C for 0.5 h, then at ambient temperature for 18 h. The solvent was removed <u>in vacuo</u> and the residue was purified by silica gel chromatography (hexane/ethyl acetate, 18 % ethyl acetate to 25 % ethyl acetate, gradient). Pure fractions were collected and the solvent evaporated <u>in vacuo</u> affording 0.29 g (48 %) of 7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.80 (bs, 2H), 7.80-7.64 (bd, 2H), 4.96-4.70 (2bs, 1H), 4.66-4.52 (m, 1H), 4.30-4.14 (bm, 1H), 4.12-4.04 (m, 2H), 4.04-3.94 (m, 2H), 3.56-3.32 (m, 2H), 2.04-1.92 (m, 1H), 1.90-1.60 (m, 4H), 1.22-1.0 (2bs, 9H).

MS: (M + 1) = 403, (M – Boc) = 303.

To the above 7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (1.1 g, 2.7 mmol) dissolved in dichloromethane (6 ml) was added 1.0 N hydrogen chloride in diethyl ether (50 ml) and the solution kept at ambient temperature for 62 h. The precipitate was filtered off and washed with diethyl ether and dried with nitrogen which afforded 0.83 g (90 %) of 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione hydrochloride as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.2-8.8 (2bs, 2H), 7.8-8.1 (m, 2H), 4,1-3.6 (m, 5H), 2.9 (bs, 1H), 2.2-1.6 (m, 5H).

MS: (M + 1) = 303.5.

To a suspension of the above 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione hydrochloride (0.7 g, 2.1 mmol) and ethyl chloroformate (0.24 ml, 2.5 mmol) in dry tetrahydrofuran (14 ml) cooled in an ice bath under nitrogen was added diisopropylethylamine (0.95 ml, 5.4 mmol) and the reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed <u>in vacuo</u> and the residue was partitioned between dichloromethane (25 ml) and 1N hydrochloric acid (25 ml). The layers were separated, and the aqueous layer extracted with

dichloromethane (20 ml). The combined organic extracts were washed with a saturated sodium bicarbonate solution (50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was triturated with n-butylchloride, filtered and dried with nitrogen which afforded 0.47 g (61 %) of 7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid ethyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (s, 2H), 7.7(s, 2H), 4.9-4.7 (2bs, 1H), 4.7-4.5 (m, 1H), 4.3-3.9 (m, 5H), 3.9-3.6 (bs, 1H), 3.6-3.3 (m, 2H), 2.0-1.9 (m, 1H), 1.9-1.5 (m, 4H), 1.1-0.7 (2bs, 3H).

MS: (M-1) = 373.

A solution of the above 7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid ethyl ester (0.44 g, 1.2 mmol) in a mixture of 1N hydrochloric acid (18 ml) and tetrahydrofuran (18 ml) was heated a 75 °C under nitrogen with stirring for 18 h. The tetrahydrofuran was removed in vacuo and the residue was extracted with dichloromethane (2 x 75 ml). The combined organic extracts were washed with a saturated sodium bicarbonate solution (50 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo affording 0.42 g (> 100 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid ethyl ester as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (s, 2H), 7.8 (s, 2H), 5.3-5.0 (bm, 1H), 4.6-4.2 (bm, 1H), 4.0 (m, 2H), 3.8-3.6 (bm, 3H), 2.8 (m, 1H), 2.7-2.4 (bm, 3H), 1.0 (bs, 3H).

MS: (M+1)= 330.56.

A mixture of the above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid ethyl ester (0.39 g, 1.2 mmol), *tert*-butyl cyanoacetate (0.22 g, 1.55 mmol), sulfur (42 mg, 1.3 mmol) in ethanol (1.5 ml) was degassed. To this mixture, under nitrogen, morpholine (205 μl) was added and the mixture was heated a 50 °C for 13 hours. The solvent was removed in vacuo. The residue (0.74 g) was purified by silica gel chromatography using a mixture of hexane/ethyl acetate (7:3) as eluant. Pure fraction were collected and the solvent evaporated in vacuo. The residue (0.29 g) was titurated with acetonitrile, filtered, and dried with

nitrogen affording 84 mg (15 %) of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester.

^{1}H MNR (400 MHz, $CDCl_3$) δ 7.9-7.7 (2m, 4H), 6.0 (bs, 2H), 5.1-4.8 (bm, 1H), 4.8-4.5 (m, 1H), 4.5-4.2 (m, 1H), 4.1-3.4 (3m, 4H), 3.0 (m, 2H), 1.8-1.4 (m, 10H), 1.1-0.9 (m, 3H).

MS: (M + 1) = 486.

To the above 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (48 mg, 0.1 mmol) dissolved in dry tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.4 ml) and the solution stirred for 18 h. at ambient temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (25 ml) and a saturated sodium bicarbonate solution (25 ml) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (25 ml). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (63 mg) was dissolved in ethyl acetate and passed through 1 g of silica gel and the solvent evaporated in vacuo affording 55 mg (90 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester as a solid.

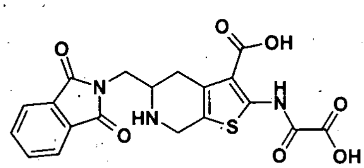
The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (55 mg, 0.09 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (2 ml) and stirred at ambient temperature for 18 h. The volatiles were removed in vacuo and the residue was purified by preparative hplc (column: Kromasil C18, 250 x 4.6 mm., flow: 2 ml/min., gradient: acetonitrile/water, 20 % acetonitrile to 60 % acetonitrile over 20 min.) affording after evaporation in vacuo 13.8 mg

(31 %) of the title compound as a solid. (Kromasil™ available from e.g. Richard Scientific Inc, Novato CA.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14-13 (bs, 1H), 12.4 (s, 1H), 7.9 (s, 4H), 4.9 (m, 2H), 4.4 (m, 1H), 4.0-2.8 (m, 13H), 0.8 (m, 3H).

MS: (M + 1) = 502.

EXAMPLE 49



5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (353 mg, 0.88 mmol) was cooled in an ice bath and then dissolved in a solution of 20 % trifluoroacetic acid/dichloromethane (7 ml). The reaction was stirred for 5 minutes in the ice bath then another 3 hours. at ambient temperature, after which it was concentrated in vacuo affording a solid residue. To the solid was added 2N hydrochloric acid (9 ml) and the mixture was heated at 50 °C (oil bath) with stirring for 24 h. The cooled reaction mixture was quenched with saturated sodium bicarbonate solution until the pH was basic. The aqueous layer was extracted with chloroform (3 x 20 ml) and the combined organic extracts dried (K_2CO_3), filtered, and the solvent evaporated in vacuo to give 205 mg (91 %) of 2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.83 (m, 2H), 7.78-7.71 (m, 2H), 3.81-3.73 (m, 2H), 3.43-3.35 (m, 1H), 3.30-3.22 (m, 1H), 2.83 (dt, J = 13, 3, 1H), 2.46 (d, J = 15, 1H), 2.42-2.32 (m, 2H), 2.21 (dd, J = 14, 13, 1H).

APCI-MS: $[M+H]^+$ = 259

The above 2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione (0.20 g, 0.76 mmol) was dissolved in dichloromethane (5 ml). Saturated sodium bicarbonate solution (5 ml) was added followed by di-*tert*-butyl dicarbonate (0.20 g, 0.91 mmol). The reaction was stirred vigorously for 16 h. after which the organic phase was separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic extracts were dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 10% gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.23 g (85 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (bs, 2H), 7.72 (bs, 2H), 5.15-4.98 (m, 1H), 4.23-4.14 (m, 1H), 3.90 (t, J = 12, 1H), 3.61-3.52 (m, 2H), 2.78-2.70 (m, 1H), 2.57-2.39 (m, 3H), 1.15 (s, 9H)

APCI-MS: $[M+H]^+ = 359$

The above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (0.43 g, 1.2 mmol) was dissolved in absolute ethanol (9 ml). To the solution was added sulfur (42 mg, 1.32 mmol) and *tert*-butyl cyanoacetate (0.22 g, 1.56 mmol). The mixture was placed under nitrogen and stirred in a 50 °C oil bath. Morpholine (0.21 ml, 2.4 mmol) was added and the reaction was stirred for 16 h. The precipitate formed was filtered off and washed with acetonitrile (2 x 3 ml) and dried which afforded 0.18 g of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester **(A)** (30 %). The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography using a gradient of ethyl acetate/hexane (1:4 to 1:3 gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 0.3 g of a mixture of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(1,3-dioxo-1,3-

dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester. HPLC purification of a small portion of the mixture gave 28 mg of pure 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester **(B)**.

(A):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.82 (m, 2H) 7.73-7.66 (m, 2H), 6.00 (bs, 2H), 5.02-4.87 (m, 1H), 4.72-4.21 (m, 2H), 4.03-3.93 (m, 1H), 3.51 (t, J = 14, 1H), 2.97-2.91 (m, 2H), 1.56 (s, 9H), 1.12-1.09 (s, 9H).

LC-MS: R_t=3.96 min, $[M+H]^+$ = 514.4

(B):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.82 (m, 2H), 7.74-7.66 (m, 2H), 5.39-5.19 (m, 1H), 4.30-4.02 (m, 2H), 3.78-3.70 (m, 1H), 3.33-3.18 (m, 1H), 2.86 (dd, J = 18, 4, 1H), 2.75-2.61 (m, 1H), 1.54 (s, 9H), 1.13-1.05 (s, 9H).

LC-MS: R_t=4.01 min, $[M+H]^+$ = 514.4

To a solution of the above 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (50 mg, 0.097 mmol) in dichloromethane (3 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (60 mg, 0.29 mmol). The reaction was placed under nitrogen and stirred for 3 hours. at ambient temperature. The solution was concentrated in vacuo and the residue purified by silica gel chromatography using a 5 % mixture of ethyl acetate/ dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 54 mg (87 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.85 (bs, 2H), 7.74-7.67 (m, 2H), 5.08-4.92 (m, 1H), 4.93-4.40 (m, 2H), 3.97-3.87 (m, 1H), 3.53 (t, J = 14, 1H), 3.11-2.99 (m, 2H), 1.62 (s, 18H), 1.14-1.12 (2s, 9H).

APCI-MS: $[M-H]^-$ = 641

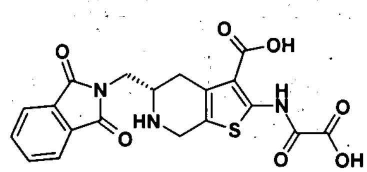
The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (54 mg, 0.084 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane, filtered off and dried in vacuo which afforded 41 mg (90 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.36 (bs, 2H), 7.93-7.90 (m, 2H), 7.88-7.85 (m, 2H), 4.43 (d, J = 16, 1H), 4.26 (d, J = 16, 1H), 4.03-3.91 (m, 2H), 3.83-3.76 (m, 1H), 3.31 (dd, J = 18, 4, 1H), 2.82 (dd, J = 18, 10, 1H).

APCI-MS: $[M+H]^+$ = 430

HPLC (254.4nm): R_t=6.72 min, 98 %

EXAMPLE 50



(L)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of L-aspartic acid (120 g, 0.90 mol) in methanol (600 ml) cooled to -20 °C was added thionylchoride (93 ml, 1.29 mol) dropwise over 0.5 h. The cooling bath was removed and the mixture was stirred for 1 h, before diethyl ether (1.8 L, containing 50 ml 1 N hydrochloric acid in diethyl ether) was added upon cooling. The resulting precipitate was filtered off and washed with diethyl ether. The product was recrystallized twice:

First recrystallization: The product was dissolved in warm methanol (600 ml) and reprecipitated with 1.8 ml diethyl ether (containing 50 ml 1 N hydrochloric acid in diethyl ether).

Second recrystallization: The product was dissolved in warm methanol (250 ml) and reprecipitated with 1.0 m diethyl ether (containing 50 ml 1 N hydrochloric acid in diethyl ether).

This afforded 75 g (45 %) of L-aspartic acid β-methyl ester hydrochloride as a solid.

To a solution of the above β-methyl ester (50 g, 0.27 mol) in water (120 ml) cooled to 0 °C was added triethylamine (95 ml, 0.68 mol) and methyl acrylate (74 ml, 0.82 mol). The reaction mixture was stirred for 3 hours before the cooling bath was removed. After stirring for an additional 1 h the mixture was washed with petrol ether (2 x 400 ml), before *tert*-butanol (40 ml) and di-*tert*-butyl dicarbonate (74 g, 0.34 mol) was added and the reaction mixture was stirred for 16 h. The mixture was washed with petrol ether (2 x 400 ml), cooled to 0 °C and the pH was adjusted to 3 with concentrated hydrochloric acid. After extraction with ethyl acetate (3 x 200 ml) the organic phase was washed with brine (200 ml), dried ($MgSO_4$), filtered and the volatiles evaporated in vacuo. The residue was subjected to column chromatography on silicagel using a mixture of ethyl acetate/hexane/methanol/acetic acid (25:25:2.5:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo which afforded 60 g (66 %) of 2-(*tert*-butoxycarbonyl-(2-methoxycarbonyl-ethyl)-amino)-succinic acid 4-methyl ester as a solid.

To a solution of the above di-ethyl ester (96.9 g, 0.29 mol) in dry degassed tetrahydrofuran (1.0 l) was added sodium methoxide (161 ml, 30% solution in methanol) and the reaction mixture was refluxed under nitrogen for 16 h with mechanical stirring. The reaction mixture was cooled to room temperature, the volatiles remove in vacuo until a wet cage was observed. Water (500 ml) was added and the reaction mixture was refluxed for 16 h. The remaining organic solvents were evaporated in vacuo before the pH was adjusted to 2.5 with concentrated hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3 x 300 ml) and the combined organic phases were washed with brine (100 ml), dried ($MgSO_4$) and filtered. *tert*-Butyl amine (25.36 g, 0.350 mol) was added

dropwise under stirring whereupon a off white precipitate was formed. The precipitate was filtered off and washed with ethyl acetate, dried in vacuo affording 74.4 g (81 %) of 4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester, *tert*-butyl amine salt as a solid.

Analytically pure compound can be obtained from recrystallisation of the crude product from ethanol-diisopropyl ether by heating the compound in ethanol (ca 100 ml per 10 g compound) and while still hot diisopropyl ether is added (ca 250 ml per 10 g compound). Yield in recrystallisation is approximately 50 %.

A solution of the above 4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester, *tert*-butyl amine salt (3.0 g, 9.48 mmol), *tert*-butyl cyanoacetate (2.01g, 14.22 mmol), sulfur (0.456 g, 14.22 mmol) and diisopropyl-ethylamine (1.64 ml, 9.48 mmol) was heated to 50 °C under nitrogen for 12 h. The orange-yellow solution was allowed to cool to room temperature before a small precipitate was filtered off. The filtrate was evaporated in vacuo and the residue was divided between ethyl acetate (50 ml) and saturated ammonium chloride (100 ml). The aqueous phase was extracted with ethyl acetate (3 x 50 m) and the combined organic phases were washed with brine (50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to column chromatography using a mixture of petrol ether/ethyl acetate/methanol (8:4:1) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 2.22 g (58 %) of 2-amino-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,5,6-tricarboxylic acid 3,6-di-*tert*-butyl ester as a solid.

To a solution of the above 3,5,6-tricarboxylic acid 3,6-di-*tert*-butyl ester (0.63 g, 1.58 mmol) in dimethoxyethane (10 ml) cooled to -20 °C was added N-methylmorpholine (174 ml, 1.58 mmol) followed by isobutylchoroformate (205 ml, 1.58 mmol) and the reaction mixture was stirred for two min. before a precipitate was filtered off. The precipitate was rapidly washed with dimethoxyethane (2 x 2.5 ml), recooled to -20 °C

and a solution of sodium borohydride (90 mg, 2.37 mmol) in water (1 ml) was added in one lot. (Caution - gas evolution).
The reaction mixture was stirred until gas evolution ceases (app. 3 min.) and the mixture was poured into water (25 ml) and extracted with ethyl acetate (10 ml), washed with brine (5 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo affording 0.40 g (66 %) of 2-amino-5-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

To a mixture of the above 2-amino-5-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (2.00 g, 5.20 mmol), phthalimide (0.92 g, 6.24 mmol) and triphenylphosphine (1.64 g, 6.24 mmol) in dry tetrahydrofuran (30 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (0.98 ml, 6.24 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. Next day the reaction mixture was again cooled to 0 °C and phthalimide (0.46 g, 3.12 mmol), triphenylphosphine (0.82 g, 3.12 mmol) and diethyl azodicarboxylate (DEAD) (0.49 ml, 3.12 mmol) was added in sequence and the reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and the resultant solid dissolved in dichlorormethane (20 ml). The residue was subjected to flash column chromatography using a mixture of ethyl acetate/hexane (1:2) as eluant. Fractions were collected affording after evaporation in vacuo 1.0 g of the desired compound contaminated with phthalimide. Recrystallization from ethanol gave 0.23 g (9 %) of pure 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

To the above di-*tert*-butyl ester (0.20 g, 0.39 mmol) dissolved in dichloromethane (4 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.23 g, 1.17 mmol) in dichloromethane (1 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was added dichlorormethane (5 ml) and washed with 1 % hydrochloric acid (10 ml), dried (Na_2SO_4), filtered and

the organic phase evaporated in vacuo affording 0.25 g (100 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

The above tri-*tert*-butyl ester (0.25 g, 0.39 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (5 ml). The reaction was stirred at room temperature for 24 h. before diethyl ether (5 ml) was added. The precipitate was filtered off, washed with diethyl ether, dried in vacuo to give 0.150 g of a solid. NMR revealed the presence of a trace amount of material arising from incomplete deprotection. 0.100 g of the crude product was redissolved in 20 % trifluoroacetic acid in dichloromethane (5 ml), and stirred at room temperature for 24 h. before diethyl ether (5 ml) was added. The product was filtered off and washed with diethyl ether and dried in vacuo to give 0.05 g (40 %) of the title compound as a solid.

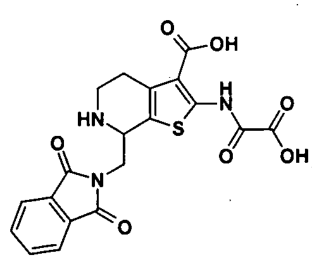
M.p.: dec.> 240° C

Calculated for $C_{19}H_{15}N_3O_7S \cdot 1/3 \cdot C_2HF_3O_2 \cdot 1/2\ H_2O$;

C, 49.58 %; H, 3.46 %; N, 8.82 %. Found:

C, 49.84 %; H, 3.83 %; N, 8.99 %.

EXAMPLE 51

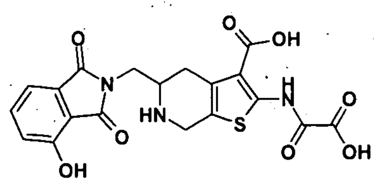


7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of pure 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (28 mg, 0.057 mmol) in dichloromethane (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (35 mg, 0.17 mmol). The reaction was placed under nitrogen and stirred for 12 h. at ambient temperature. The volatiles were evaporated in vacuo and the residue was purified by silica gel chromatography using a mixture of ethyl acetate/ hexane (1:3) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 25 mg (67 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59-12.53 (bs, 1H), 7.89-7.84 (m, 2H), 7.75-7.67 (m, 2H), 5.61-5.41 (m, 1H), 4.36-4.15 (m, 1H), 4.12-4.06 (m, 1H), 3.90-3.82 (m, 1H), 3.34-3.21 (m, 1H), 2.99-2.93 (m, 1H), 2.84-2.68 (m, 1H), 1.62-1.59 (s, 18H), 1.12-1.06 (s, 9H).

The above 2-(*tert*-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (25 mg, 0.039 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (1.5 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane, filtered off and dried in vacuo to give 41 mg (85 %) of the title compound as a solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.48 (bs, 2H), 7.95-7.91 (m, 2H), 7.89-7.84 (m, 2H), 4.89 (s, 1H), 4.15-4.07 (m, 2H), 3.43-3.28 (2m, 2H, partially obscured by water), 3.04 (bs, 2H).
LC-MS: R_t=1.51 min, $[M-H]^-$ = 428.4

EXAMPLE 52



5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (1.55 g, 3.85 mmol) was cooled in an ice bath and then dissolved in a solution of 20 % trifluoroacetic acid/dichloromethane (15 ml). The reaction was stirred and allowed to slowly warm to ambient temperature during 3 hours. The solution was concentrated in vacuo to give crude 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione which was used directly in the following step (assumed 100 % yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 8.19 (bs, 1H), 7.78-7.75 (m, 2H), 7.74-7.71 (m, 2H), 4.11-3.98 (m, 5H), 3.90-3.79 (m, 3H), 3.26-3.17 (m, 1H), 2.10-2.00 (m, 3H), 1.92-1.88 (m, 1H).

To a suspension of the above 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione (3.85 mmol) in absolute ethanol (25 ml) was added hydrazine (0.36 ml, 11.55 mmol). The reaction was stirred at 80 °C (oil bath) for 6 h., then cooled to ambient temperature and stirred for an additional 12 h. The thick precipitate was filtered off and washed with ethanol. The filtrate was concentrated in vacuo and reconstituted in dichloromethane (20 ml), forming a small amount of a second precipitate which was filtered off. The filtrate was evaporated in vacuo and the resulting oil was dissolved in water (10 ml) and basified with 1N sodium hydroxide until pH = 10. The aqueous layer was extracted with 20 % isopropyl alcohol/chloroform (12 x 40 ml). The combined organic extracts

were dried (K_2CO_3), filtered and the solvent evaporated in vacuo affording 0.42 g (63 %) of (1,4-dioxa-8-aza-spiro[4.5]dec-7-yl)methylamine as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (bs, 4H), 3.11-3.05 (m, 1H), 2.81 (dt, *J* = 12, 3, 1H), 2.76-2.65 (m, 2H), 2.58-2.50 (m, 1H), 1.70-1.57 (m, 3H), 1.31 (t, *J* = 12, 1H).
APCI-MS: $[M+H]^+$ = 173.2

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (0.51 g, 3.09 mmol) in anhydrous N,N-dimethylformamide (7 ml) under nitrogen was added sodium hydride (130 mg, 3.25 mmol). Immediate evolution of gas and bright yellow color was observed. The mixture was stirred for 5 minutes after which benzyl bromide (1.8 ml, 15.45 mmol) was added. The reaction was stirred for 72 h. Saturated sodium bicarbonate (2 ml) was added and the mixture stirred for 2 minutes, diluted in ethyl acetate (35 ml) and washed with saturated sodium bicarbonate (5 ml), 1N hydrochloric acid (5 ml), and brine (2 x 5 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. To the crude material was added hexane and the formed precipitate was filtered off, washed further with hexane and dried in vacuo to give 0.54 g (69 %) of 4-(benzyloxy)-isobenzofuran-1,3-dione as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (t, 1H, *J* = 8 Hz), 7.54 (d, 1H, *J* = 8 Hz), 7.47-7.29 (m, 6H), 5.36 (s, 2H).

A solution of (1,4-dioxa-8-aza-spiro[4.5]dec-7-yl)methylamine (0.19 g, 1.1 mmol) and 4-(benzyloxy)-isobenzofuran-1,3-dione (0.27 g, 1.05 mmol) was prepared in a mixture of distilled dichloromethane (3 ml) and anhydrous N,N-dimethylformamide (2.5 ml) under nitrogen. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.23 g, 1.21 mmol) was added followed by triethylamine (0.46 ml, 3.3 mmol) and the reaction stirred at ambient temperature for 18 h. The solution was concentrated in vacuo and the residue diluted with ethyl acetate (25 ml) and washed with water (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was evaporated in vacuo and the residue

purified by silica gel chromatography using a mixture of 5 % methanol/dichloromethane/1 % triethylamine as eluant .Pure fractions were collected and the solvent evaporated in vacuo affording 0.22 g (50 %) of 4-benzyloxy-2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione as a semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 8, 1H), 7.48 (d, *J* = 7, 2H), 7.42-7.29 (m, 4H), 7.18 (d, *J* = 8, 1H), 5.31 (s, 2H), 3.94-3.90 (m, 4H), 3.65 (d, *J* = 6, 2H), 3.16-3.09 (m, 1H), 3.07-3.02 (m, 1H), 2.76 (dt, *J* = 13, 3, 1H), 1.78 (d, *J* = 12, 1H), 1.64-1.54 (m, 3H), 1.37 (t, *J* = 12, 1H), 1.08 (t, *J* = 7, 1H).

LC-MS: R_t=2.59 min, $[M+H]^+$ = 409.2

To a solution of the above 4-benzyloxy-2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione (0.22 g, 0.54 mmol) in 1,4-dioxane (4 ml) was added 4N hydrochloric acid (4 ml) and the reaction stirred in a 65 °C (oil bath) for 6 h. The mixture was basified with saturated sodium bicarbonate until pH = 8 and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo affording crude 4-benzyloxy-2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione as an oil. Which was used without further purification or characterization.

The above crude 4-benzyloxy-2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione (0.17 g, 0.47 mmol) was dissolved in dichloromethane (4 ml). Saturated sodium bicarbonate (4 ml) was added followed by di-*tert*-butyl dicarbonate (0.11 g, 0.52 mmol). The reaction was stirred vigorously for 16 h., then the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a mixture of ethyl acetate/hexane (1:2) as eluant. Pure fractions were collected and the solvent was evaporated in vacuo affording 0.14 g (64 %) of 2-(4-

benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (bs, 1H), 7.47-7.31 (m, 6H), 7.18 (bs, 1H), 5.34 (s, 2H), 5.03 (bs, 1H), 4.45-4.14 (m, 1H), 3.89 (t, J = 12, 1H), 3.55 (bs, 2H), 2.76-2.71 (m, 1H), 2.57-2.38 (m, 3H), 1.17 (s, 9H).

A solution of 2-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (0.14 g, 0.30 mmol), sulfur (10.6 mg, 0.33 mmol), and *tert*-butyl cyanoacetate (55 mg, 0.39 mmol) in absolute ethanol (4 ml) was stirred at 50 °C (oil bath). Morpholine (53 µl, 0.6 mmol) was added and the reaction placed under nitrogen and stirred for 16 h. The solution was cooled to ambient temperature, concentrated <u>in vacuo</u> and the residue purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 5 % gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording a mixture of regioisomers 0.15 g (80 %) of 2-amino-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester which were not separable by chromatography.

To a solution of the above mixture of 2-amino-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (0.15 g, 0.24 mmol) in distilled dichloromethane (4 ml) under nitrogen was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.14 g, 0.72 mmol) and the reaction mixture was stirred at ambient temperature for 1.5 h. The volatiles were evaporated <u>in vacuo</u> and the crude residue was purified by silica gel chromatography using dichloromethane as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 50 mg of 2-(*tert*-

butoxyoxalyl-amino)-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (**A**) and 50 mg of 2-(*tert*-butoxyoxalyl-amino)-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (**B**). Another 50 mg remained as a mixture of the two isomers (**A**) and (**B**).

(A):

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.60-7.31 (m, 7H), 7.20-7.10 (m, 1H), 5.33 (s, 2H), 5.05-4.38 (m, 3H), 3.96-3.83 (m, 1H), 3.52-3.41 (m, 1H), 3.01 (bs, 2H), 1.60 (s, 9H), 1.59 (s, 9H), 1.17-1.14 (s, 9H).

LC-MS: R_t=4.93 min, $[M+H]^+$ = 748.1

(B):

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.58-12.52 (s, 1H), 7.60-7.30 (m, 7H), 7.20-7.10 (m, 1H), 5.60-5.39 (m, 1H), 5.34 (s, 2H), 4.36-4.02 (m, 2H), 3.86-3.75 (m, 1H), 3.33-3.18 (m, 1H), 2.97-2.90 (m, 1H), 2.83-2.68 (m, 1H), 1.60 (s, 9H), 1.58-1.57 (s, 9H), 1.15-1.09 (s, 9H)

LC-MS: R_t=4.93 min, $[M+H]^+$ = 748.1

The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (50 mg, 0.067 mmol) was dissolved in a mixture of ethyl acetate/ethanol (3 ml, 1:1). Palladium on activated carbon (10 %, 10 mg) was added and the solution degassed and stirred under hydrogen (1 atm.) for 72 h. TLC analysis indicated that the reaction was incomplete. The mixture was filtered through celite and the filter cake washed with hot ethyl acetate. The filtrate was concentrated in vacuo and purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 5 % gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 15 mg (30 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-

isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

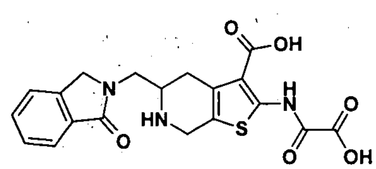
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.61-7.51 (m, 1H), 7.39-7.34 (m, 1H), 7.17-7.09 (m, 1H), 5.04-4.64 (m, 2H), 4.49-4.34 (m, 1H), 3.90-3.78 (m, 1H), 3.51-3.42 (m, 1H), 3.02 (bs, 2H), 1.60 (s, 18H), 1.17-1.14 (2s, 9H).

The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (15 mg, 0.023 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml). The reaction was stirred at ambient temperature for 12 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo affording 6 mg (47 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 11.17 (s, 1H), 9.25 (bs, 2H), 7.64 (t, J = 8, 1H), 7.32 (d, J = 8, 1H), 7.24 (d, J = 8, 1H), 4.41-4.23 (m, 2H), 3.96-3.71 (m, 3H), 3.5-3.2 (obscured by water, 1H), 2.83-2.75 (m, 1H).

LC-MS: R_t=1.53 min, $[M+H]^+$ = 446.2

EXAMPLE 53



2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-Methyl-benzoic acid methyl ester (1.50 g 10 mmol), N-bromosuccinimide (1.96 g, 11 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN) (25 mg,

0.15 mmol) were dissolved in chloroform (3 ml). The solution was heated at reflux for 16 h. cooled and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (1-2 %) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 2.05 g (89 %) of 2-bromomethyl-benzoic acid methyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, *J* = 7.6 Hz), 7.45-7.52 (m, 2H), 7.38 (dt, 1H, *J* = 1.2, 7.6 Hz), 4.96 (s, 2H), 3.95 (s, 1H).

To a solution of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (100 mg, 0.20 mmol) and pyridine (0.18 ml, 2.0 mmol) in acetonitrile (1 ml) at room temperature was added benzyl chloroformate (0.28 ml, 2.0 mmol) in 10 aliquots over 48 h. The solution was then taken into ethyl acetate (30 ml), washed with 0.5 N hydrochloric acid (3 x 10 ml), saturated sodium bicarbonate (3 x 10 ml), brine (10 ml), dried ($MgSO_4$) and filtered. The solvent was evaporated in vacuo. The resulting oil crystallized upon standing for 2 days. The precipitate was filtered off and washed with diethyl ether (3 x 1 ml) affording after drying in vacuo 59 mg (47 %) of 2-benzyloxy-carbonylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 10.60 (s, 1H), 7.60-7.92 (m, 4H), 7.38 (m, 5H), 5.26 (s, 2H), 4.30-5.10 (m, 3H), 3.40-4.00 (m, 2H), 1.57 (m, 9H), 1.15 (m, 9H).

To a solution of 1 N hydrochloric acid in ethyl acetate (1.0 ml) was added 2-benzyloxy-carbonylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (52 mg, 0.08 mmol). The solution was stirred at room temperature for 48 h. A precipitate was filtered off which afforded 42 mg (90 %) of 2-benzyloxy-carbonylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester hydrochloride as a solid.

^1H NMR (DMSO-d_6): δ 10.45 (s, 1H), 9.40 (s, 1H), 9.25 (s, 1H), 7.89 (m, 4H), 7.39 (m, 5H), 5.22 (s, 2H), 4.39 (d, 1H, J = 15 Hz), 4.28 (m, 1H), 3.95 (m, 2H), 3.79 (m, 1H), 3.20 (m, 1H), 2.70 (m, 1H), 1.48 (s, 9H).

To a solution of the above 2-benzyloxy-carbonylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester hydrochloride (42 mg, 0.072 mmol) in ethanol (0.5 ml) was added hydrazine (68 μl, 0.22 mmol). The solution was stirred at 80 °C for 5 h. and at room temperature for 16 h. The mixture was filtered and the filtrate evaporated <u>in vacuo</u>. The residue was extracted with dichloromethane (5 x 1 ml). The combined dichloromethane washes were evaporated <u>in vacuo</u> affording 20 mg (67 %) of 5-aminomethyl-2-benzyloxy-carbonylamino-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
^1H NMR ($CDCl_3$): δ 10.55 (bs, 1H), 7.37 (m, 5H), 5.23 (s, 2H), 3.92 (s, 2H), 2.60-3.10 (m, 3H), 1.53 (s, 9H).

To a solution of the above 5-aminomethyl-2-benzyloxy-carbonylamino-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (20 mg, 0.048 mmol) in acetonitrile (1 ml) at 0 °C was added diisopropylethylamine (18 μl, 0.15 mmol) and 2-bromomethyl-benzoic acid methyl (12 mg, 0.048 mmol). The solution was stirred at 0 °C for 3 hours. and at room temperature for 16 h. Di-*tert*-butyl dicarbonate (21 mg, 0.096 mmol) was then added to the solution. The solution was then stirred at room temperature for 16 h. The solution was taken into ethyl acetate (30 ml), washed with 0.5 N hydrochloric acid (3 x 10 ml), saturated sodium bicarbonate (3 x 10 ml) and brine (10 ml), dried ($MgSO_4$) and filtered. The solvent was evaporated <u>in vacuo.</u> The solid residue was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/hexane as eluant. Pure fractions were collected and the solvent evaporated <u>in vacuo</u> affording 10 mg (33 %) of 2-benzyloxycarbonylamino-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 10.59 (s, 1H), 7.81 (m, 1H), 7.52 (m, 1H), 7.39 (m, 7H), 5.25 (s, 1H), 4.22-5.00 (m, 4H), 4.40-4.80 (m, 2H), 2.80-3.10 (m, 2H), 1.55 (s, 9H), 1.25 (s, 9H).

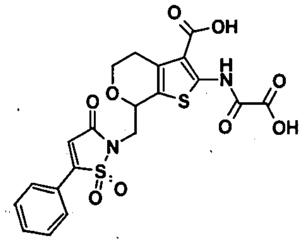
To a solution of the above 2-benzyloxycarbonylamino-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (9 mg, 0.014 mmol) in methanol (2 ml) was added 10 % Pd/C (4 mg). The mixture was stirred under hydrogen (1 atm.) for 3 hours. and then filtered. The filtrate was evaporated in vacuo affording 6 mg (93 %) of 2-amino-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 7.80 (m, 1H), 7.50 (m, 1H), 7.44 (m, 2H), 4.22-5.00 (m, 4H), 4.40-4.80 (m, 2H), 2.80-3.10 (m, 2H), 1.63 (s, 9H), 1.25 (s, 9H).

To a solution of the above 2-amino-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (6 mg, 0.013 mmol) in acetonitrile (0.5 ml) at room temperature was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (27 mg, 0.13 mmol). The solution was stirred for 3 hours. at room temperature and then diluted with ethyl acetate (20 ml), washed with 0.5 N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 5 ml), brine (5 ml), dried ($MgSO_4$) and filtered. The solvent was evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25 % gradient) as eluant. Pure fractions were collected and the solvent evaporated in vacuo affording 4 mg (50 %) of 2-(*tert*-butoxyoxalyl-amino-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H NMR ($CDCl_3$): δ 12.49 (s, 1H), 7.80 (m, 1H), 7.50 (m, 1H), 7.44 (m, 2H), 4.22-5.00 (m, 4H), 4.20-4.90 (m, 2H), 2.90-3.20 (m, 2H), 1.63 (s, 9H), 1.60 (s, 9H), 1.25 (s, 9H).

EXAMPLE 55



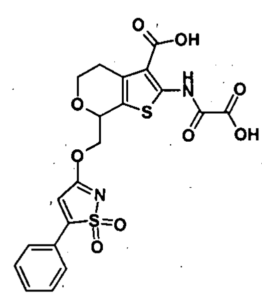
2-(Oxalyl-amino)-7-(1,1,3-trioxo-5-phenyl-1,3-dihydro-isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-7-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxo-5-phenyl-1,2-dihydro-1H-isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

^{1}H-NMR (DMSO-d_6) δ 2.85 (bs, 2H), 3.75 (m, 1H), 3.92 (dd, 1H), 4.10 (m, 2H), 5.08 (m, 1H), 7.64 (m, 3H), 7.69 (s, 1H), 7.92 (m, 2H), 12.35 (s, 1H, N*H*CO).

LC-MS: R_t = 4.90 min, m/z: 493 $[M+H]^+$

EXAMPLE 56



7-(1,1-Dioxo-5-phenyl-1*H*-isothiazol-3-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

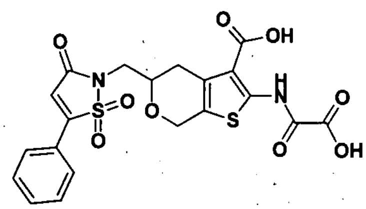
The title compound was prepared in a similar way as described in Example 23 using 2-amino-7-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxo-5-phenyl-1,2-

dihydro-1*H*-isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

^{1}H-NMR (DMSO-d_6) δ 2.86 (bs, 2H), 3.79 (m, 1H), 4.13 (m, 1H), 4.75 (m, 2H), 5.17 (bs, 1H), 7.60 (m, 3H), 7.70 (s, 1H), 7.88 (m, 2H), 12.35 (s, 1H, N*H*CO).

LC-MS: R_t = 4.78 min, m/z: 493 $[M+H]^+$

EXAMPLE 57

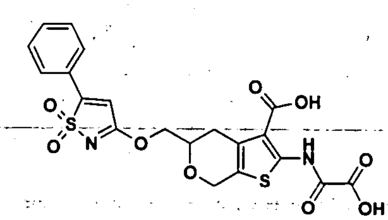


2-(Oxalyl-amino)-5-(1,1,3-trioxo-5-phenyl-1,3-dihydro-isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxo-5-phenyl-1,2-dihydro-1*H*-isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

^{1}H-NMR (DMSO-d_6) δ 2.62 (dd, 1H), 3.05 (d, 1H), 3.88 (m, 2H), 3.98 (m, 1H), 4.60–4.86 (dd, 2H), 7.66 (m, 4H), 7.93 (m, 2H), 12.3 (s, 1H, N*H*CO).

EXAMPLE 58



5-(1,1-Dioxo-5-phenyl-1*H*-isothiazol-3-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxo-5-phenyl-1,2-dihydro-1*H*-isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

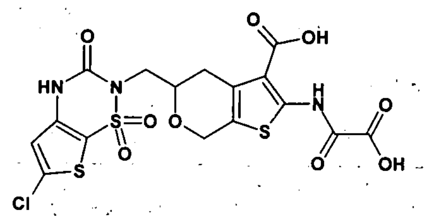
Mp.: 230 - 232 °C;

Calculated for $C_{20}H_{16}N_2O_9S_2$, $1xH_2O$;

C, 47.06 %; H, 3.55 %; N, 5.49 %. Found:

C, 46.88 %; H, 3.44 %; N, 5.45 %.

EXAMPLE 59

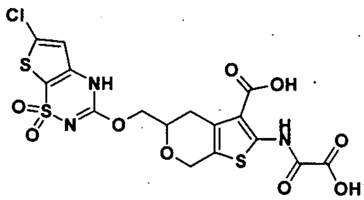


5-(6-Chloro-1,1,3-trioxo-2,3-dihydro-4*H*-thieno[3,2-e]-1,2,4-thiadiazin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxide-6-chloro-2,3-dihydro-4*H*-thieno[3,2-e]-1,2,4-thiadiazine-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

^{1}H-NMR (DMSO-d_6) δ 2.60 (dd, 1H), 2.98 (d, 1H), 3.87–3.96 (m, 2H), 4.04 (m, 1H), 4.56–4.82 (dd, 2H), 7.0 (s, 1H), 11.95 (s, 1H, N*H*CO), 12.3 (s, 1H, N*H*CO).

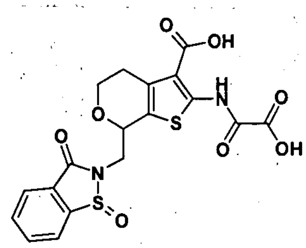
EXAMPLE 60



5-(6-Chloro-1,1-dioxo-4*H*-thieno[3,2-e]-1,2,4-thiadiazine-3-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1,1-dioxide-6-chloro-2,3-dihydro-4*H*-thieno[3,2-e]-1,2,4-thiadiazine-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.
Mp.: > 250 °C;
Calculated for $C_{16}H_{12}ClN_3O_9S_3$, $0.75xH_2O$;
C, 35.89 %; H, 2.54 %; N, 7.85 %. Found:
C, 35.84 %; H, 2.36 %; N, 7.74 %.

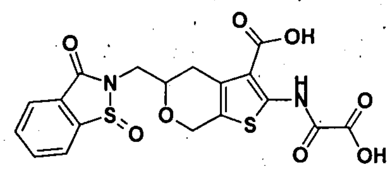
EXAMPLE 61



7-(1,3-Dioxo-1,3-dihydro-benzo[d]isothiazol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-7-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1-oxo-1,2-dihydro-1H-benzo[d]isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.
LC-MS: R_t = 3.82 min, m/z: 451 $[M+H]^+$

EXAMPLE 62

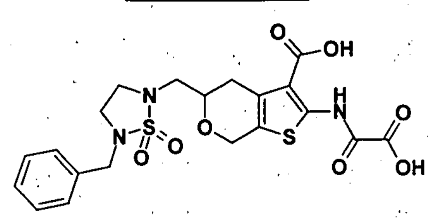


5-(1,3-Dioxo-1,3-dihydro-benzo[d]isothiazol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 1-oxo-1,2-dihydro-1*H*-benzo[d]isothiazol-3-one as starting material. *O*- and *N*-alkylated products were separated by column chromatography.

Mp.: 230 - 231 °C;
Calculated for $C_{18}H_{14}N_2O_8S_2$, 0.5xH_2O;
C, 47.06 %; H, 3.29 %; N, 6.10 %. Found:
C, 46.94 %; H, 3.42 %; N, 6.26 %.

EXAMPLE 63

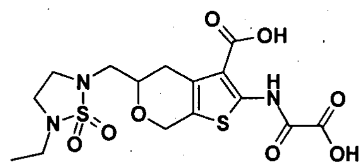


5-(5-Benzyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-benzyl-[1,2,5]thiadiazolidine 1,1-dioxide as starting material.
Mp.: 188 - 192 °C;

LC-MS: R_t = 5.00 min, m/z: 496 $[M+H]^+$

EXAMPLE 64

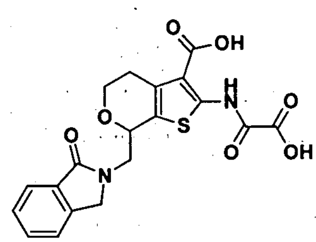


5-(5-Ethyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 23 using 2-amino-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-ethyl-[1,2,5]thiadiazolidine 1,1-dioxide as starting material.

LC-MS: R_t = 4.18 min, m/z: 434 $[M+H]^+$

EXAMPLE 65



2-(Oxalyl-amino)-7-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-7-aminomethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (100 mg, 0.38 mmol) and *N,N*-

diisopropylethylamine (72 μL, 0.41 mmol) in acetonitrile (6 ml) at 0 °C was added 2-bromomethyl-benzoic acid methyl ester (43 mg, 0.19 mmol). The reaction mixture was stirred for 16 hours and the solvent evaporated in vacuo. The residue was diluted in ethyl acetate (50 ml), washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo, which afforded 50 mg (68 %) of 2-amino-7-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 7.86 (d, 1H, *J* = 8 Hz), 7.55 (t, 1H, *J* = 8 Hz), 7.45 (t, 2H, *J* = 8 Hz), 4.88 (dt, 1H. *J* = 6, 2 Hz), 4.68 (d, 1H, *J* = 17 Hz), 4.48 (d, 1H, *J* = 17 Hz), 4.25-4.10 (m, 1H), 4.03 (dd, 1H, *J* = 17 and *J* = 3 Hz), 3.80-3.75 (m, 2H), 2.92-2.70 (m, 2H), 1.54 (s, 9H).

To a solution of 2-amino-7-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (50 mg, 0.13 mmol) in tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (100 mg, 0.51 mmol). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (50 ml), washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was chromatographed using a mixture of 10% ethyl acetate/dichloromethane as eluent, which afforded 55 mg (83 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 12.59 (s, 1H), 7.88 (d, 1H, *J* = 7 Hz), 7.54 (t, 1H, *J* = 7 Hz), 7.46 (t, 2H, *J* = 7 Hz), 5.04 (dd, 1H, *J* = 6 Hz and *J* = 2 Hz), 4.69 (d, 1H, *J* = 17 Hz), 4.46 (d, 1H, *J* = 17 Hz), 4.26-4.10 (m, 2H), 3.77 (dd, 1H, *J* = 9 Hz and *J* = 3 Hz), 3.70 (dd, 1H, *J* = 15 Hz and *J* = 9 Hz), 3.02-2.80 (m, 2H), 1.55 (s, 18H).

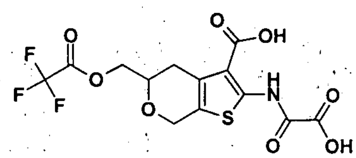
A solution of 2-(*tert*-butoxyoxalyl-amino)-7-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl

ester (55 mg, 0.11 mmol) in 50 % trifluoroacetic acid/dichloromethane (2 ml) was stirred for 16 hours. The volatiles were removed in vacuo and the residue was washed with dichloromethane and dried, which afforded 29 mg (50 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6) δ 12.35 (s, 1H), 7.70 (d, 1H, J = 8 Hz), 7.61 (d, 1H, J = 3 Hz), 7.52-7.47 (m, 2H), 5.04 (s, 1H), 4.59 (d, 1H, J = 18 Hz), 4.58 (d, 1H, J = 18 Hz), 4.19-4.08 (m, 1H), 3.88 (d, 1H, J = 6 Hz), 3.78-3.66 (m, 1H), 3.38 (q, 1H, J = 7 Hz), 2.85 (s, 2H);

LC-MS: R_t = 2.12 min, m/z: 417 $[M+H]^+$.

EXAMPLE 66



2-(Oxalyl-amino)-5-(2,2,2-trifluoro-acetoxymethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

2-(*tert*-Butoxyoxalyl-amino)-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.5 g, 1.21 mmol) was dissolved in dichloromethane (9 ml) and trifluoroacetic acid (3 ml) was added. The reaction mixture was stirred 64 hours at room temperature. The precipitate was filtered off and washed with diethyl ether and dried in vacuo at 50 °C for 4 hours, which afforded 180 mg (50 %) of the title compound as a solid.

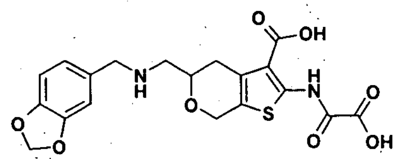
Mp.: 231 - 233 °C;

Calculated for $C_{13}H_{10}F_3NO_8S$;

C, 39.30 %; H, 2.56 %; N, 3.57 %. Found:

C, 39.30 %; H, 2.54 %; N, 3.53 %.

EXAMPLE 67



<u>5-(((Benzo[1,3]dioxol-5-ylmethyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid</u>

To a solution of oxalyl chloride (1 ml, 11.13 mmol) in dichloromethane (40 ml) cooled to –78 °C under an atmosphere of nitrogen was added dropwise a solution of dimethylsulfoxide (1.6 ml, 21.78 mmol) in dichloromethane (16 ml) during 5 min. After stirring for 15 min at –78 °C a solution of 2-(*tert*-butoxyoxalyl-amino)-5-hydroxymethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (2.0 g, 4.84 mmol) in dichloromethane (30 ml) was added dropwise and the resulting mixture was stirred for 0.5 hour at –78 °C. *N,N*-Diisopropylethylamine (4.2 ml, 24.18 mmol) was added and the reaction mixture allowed reaching room temperature at which time heptane (700 ml) was added. The mixture was filtered through anhydrous sodium sulfate and the solvent evaporated <u>in vacuo</u>. The residue (2.71 g) was purified on column chromatography using a mixture of ethyl acetate/heptane (1:4) as eluent which afforded 0.93 g (47 %) of 2-(*tert*-butoxyoxalyl-amino)-5-formyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

To a mixture of 2-(*tert*-butoxyoxalyl-amino)-5-formyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.46 g, 1.12 mmol) and piperonylamine (145 μl, 1.12 mmol) in 1,2-dichloroethane (25 ml) was added sodium triacetoxyborohydride (0.35 g, 1.57 mmol) and the resulting mixture was stirred at room temperature for 1 hour. The mixture was washed with saturated aqueous sodium hydrogencarbonate (2 x 30 ml) and dried (Na_2SO_4), filtered and the solvent evaporated <u>in</u> <u>vacuo</u>. The residue (0.56 g) was purified on column chromatography using a mixture of ethyl acetate/heptane (1:1) as eluent followed by a mixture of 10% triethylamine in ethyl acetate/heptane (1:1) as eluent. Semi pure fractions were collected and the solvent evaporated <u>in vacuo</u>. The residue (180 mg) was subjected to preparative TLC using a mixture of 10% triethylamine in ethyl acetate/ethanol (4:1) as eluent. The desired band was taken off and

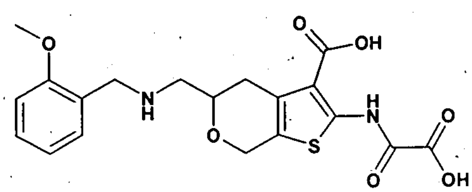
extracted with methanol (400 ml) for 0.5 hour, filtered and the solvent evaporated in vacuo, which afforded 250 mg (> 100%, contains dichloromethane and silicagel) of 5-(((benzo[1,3]dioxol-5-ylmethyl)-amino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS: R_t = 5.75 min, m/z: 547 $[M+H]^+$.

5-(((Benzo[1,3]dioxol-5-ylmethyl)-amino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (250 mg) was dissolved in dichloromethane (9 ml) and trifluoroacetic acid (3 ml) was added. The reaction mixture was stirred 16 hours at room temperature. The volatiles were evaporated in vacuo and the residue triturated with a small portion of diethyl ether. The solid precipitate was filtered off and washed with diethyl ether and dried in vacuo at 50 °C for 16 hours, which afforded 160 mg of the title compound as a solid.

Calculated for $C_{19}H_{18}N_2O_8S$, 2xTFA, $3xH_2O$;
C, 38.56 %; H, 3.66 %; N, 3.91 %. Found:
C, 38.61 %; H, 3.90 %; N, 4.22 %.

EXAMPLE 68

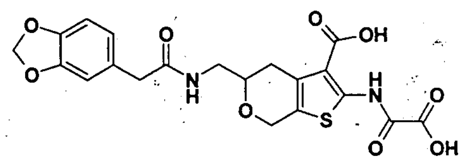


5-((2-Methoxy-benzylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 66 using 2-(*tert*-butoxyoxalyl-amino)-5-formyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-methoxy-benzylamine as starting material.

Calculated for $C_{19}H_{20}N_2O_7S$, 0.75xTFA;
C, 48.67 %; H, 4.13 %; N, 5.54 %. Found:
C, 48.61 %; H, 4.42 %; N, 5.35 %.

EXAMPLE 69)



5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 3,4-methylenedioxy phenylacetic acid (0.22 g, 1.09 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (0.27 g, 1.42 mmol) in acetonitrile (6 ml) was added triethylamine (0.46 ml, 3.27 mmol). The resultant mixture was allowed to stir at ambient temperature for 10 min. before 2-amino-5-aminomethyl-4,7-dihydro-5*H*-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.311 g, 1.09 mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 18 hours and then concentrated in vacuo. To the residue ethyl acetate and water were added and the layers separated. The organic layer was washed with hydrochloric acid (0.5M, (v/v)), saturated sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The crude 2-amino-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)-methyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was used immediately in the next step.

^{1}H-NMR ($CDCl_3$) δ 6.78-6.69 (m, 3H), 5.97 (bs, 2H), 5.95 (s, 2H), 4.60-4.58 (m, 1H), 4.53 (s, 2H), 3.73 (ddd, 1H, J = 14 Hz, J = 7.6 Hz and J = 3.2 Hz), 3.65-3.59 (m, 1H), 3.49 (s, 2H), 3.11 (ddd, 1H, J = 12.4 Hz, J = 4 Hz and J = 4.4 Hz), 2.76 (dm, 1H), 2.44 (ddt, 1H, J = 19.6 Hz, J = 13.2 Hz and J = 2.4 Hz), 1.51 (s, 9H).

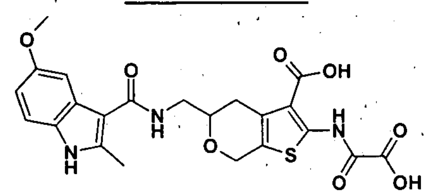
To a solution of the above crude 2-amino-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)-methyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.17 g, 0.38 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.22 g, 1.14 mmol). The reaction mixture was stirred at room temperature for 18 hours, the volatiles evaporated in vacuo and the residue diluted with ethyl acetate. The organic layer was washed with hydrochloric acid (1% (v/v), 2 x 25 ml), saturated sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue subjected to flash chromatography using a mixture of ethyl acetate/hexanes (1:2) as eluent, which afforded 0.12 g (55 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)-methyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H-NMR ($CDCl_3$) δ 12.51 (bs, 1H), 6.78 (d, 1H, J = 8 Hz), 6.77 (d, 1H, J = 1.6 Hz), 6.71 (dd, 1H, J = 8.4 Hz and J = 1.6 Hz), 5.96 (s, 2H), 4.70 (m, 2H, J = 35 Hz, J = 15.2 Hz, J = 14.4 Hz and J = 2 Hz), 3.77 (ddd, 1H, J = 10.8 Hz, J = 7.6 Hz and J = 3.2 Hz), 3.67-3.62 (m, 1H), 3.50 (s, 2H), 3.15 (ddd, 1H, J = 12.8 Hz, J = 8.4 Hz and J = 4.4 Hz), 2.87 (dt, 1H, J = 16 Hz and J = 3 Hz), 2.57-2.50 (m, 1H), 1.61 (s, 9H), 1.57 (s, 9H);
LC-MS: m/z: 575.0 $[M+H]^+$

2-(*tert*-Butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)-methyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.12 g, 0.20 mmol) was dissolved in a 50% solution of trifluoroacetic acid/dichloromethane (2 ml). The reaction mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo to 1/5 of the volume and

the precipitate filtered off and washed with dichloromethane (2x) affording 50 mg (50 %) of the title compound as a solid.

^{1}H-NMR (DMSO-d_6) δ 12.32 (bs, 1H), 8.20 (t, 1H, J = 6.8 Hz), 6.81 (m, 2H), 6.70 (m, 1H), 5.95 (s, 2H), 4.80 (d, 1H, J = 19.6 Hz), 4.63 (d, 1H, J = 20 Hz), 3.65 (m, 1H), 3.34 (s, 2H), 3.30-3.20 (m, 3H), 2.87 (dm, 1H); LC-MS: m/z: 463.0 $[M+H]^+$.

EXAMPLE 70



5-(((5-Methoxy-2-methyl-1*H*-indol-3-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 5-methoxy-2-methyl indole-3-acetic acid (0.26 g, 1.18 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (0.27 g, 1.4 mmol) in acetonitrile (10 ml) was added triethylamine (0.46 ml, 3.2 mmol). The reaction mixture was allowed to stir for 10 min at room temperature before compound 2-amino-5-aminomethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.307 g, 1.08 mmol) was added. The reaction mixture was allowed to stir for 18 hours and then concentrated in vacuo. Ethyl acetate and water were added and the layers separated. The organic layer was washed with hydrochloric acid (0.5M, (v/v)), saturated sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude 2-amino-5-(((5-methoxy-2-methyl-1*H*-indol-3-carbonyl)amino)-methyl)-4,7-

dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was used immediately in the next step.

^{1}H-NMR ($CDCl_3$) δ 7.90 (bs, 1H), 7.19 (d, 1H, *J* = 8.8 Hz), 6.87 (d, 1H, *J* = 2.4 Hz), 6.79 (dd, 1H, *J* = 8.8 Hz and *J* = 2.4 Hz), 6.18 (m, 1H), 5.94 (s, 2H), 4.33 (m, 2H, *J* = 25 Hz, *J* = 14 Hz, *J* = 2.8 Hz and *J* = 1.6 Hz), 3.80 (s, 3H), 3.76 (ddd, 1H, *J* = 14 Hz, *J* = 8 Hz and *J* = 2.8 Hz), 3.65 (s, 3H), 3.53 (m, 1H), 2.99 (ddd, 1H, *J* = 13 Hz, *J* = 5.6 Hz and *J* = 4 Hz), 2.76 (dt, 1H, *J* = 16.8 Hz, *J* = 2.8 Hz), 2.42-2.40 (m, 1H), 2.38 (s, 3H), 1.51 (s, 9H).

To a solution of the crude 2-amino-5-(((5-methoxy-2-methyl-1*H*-indol-3-carbonyl)amino)methyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.35 g, 0.72 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.42 g, 2.1 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and the residue diluted with ethyl acetate. The organic layer was washed with hydrochloric acid (1% (v/v), 2 x 25 ml), saturated sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue subjected to flash chromatography using a mixture of ethyl acetate/hexanes (1:1) as eluent, which afforded 0.24 (55 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(((5-methoxy-2-methyl-1*H*-indol-3-carbonyl)amino)methyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 12.50 (bs, 1H), 7.92 (s, 1H), 7.20 (dd, 1H, *J* =8.4 Hz and *J* = 0.4 Hz), 6.88 (d, 1H, *J* = 2.4 Hz), 6.80 (dd, 1H, *J* = 8.8 Hz and *J* = 2.4 Hz), 6.21 (m, 1H), 4.56 (dd, 1H, *J* = 14.8 Hz and *J* = 2.8 Hz), 4.44 (dt, 1H, *J* = 14.4 Hz and *J* = 2.8 Hz), 4.11 (q, 1H, *J* = 7.2 Hz), 3.81-3.75 (m, 1H), 3.79 (s, 3H), 3.66 (s, 2H), 3.58-3.54 (m, 1H), 3.01 (ddd, 1H, *J* = 14 Hz, *J* = 8.8 Hz and *J* = 4.4 Hz), 2.85 (dt, 1H, *J* = 16.8 Hz and *J* = 6 Hz), 2.52-2.45 (m, 1H), 2.38 (s, 3H), 1.60 (s, 9H), 1.57 (s, 9H);

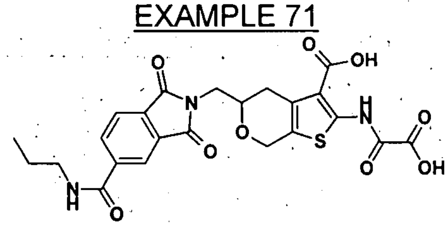
LC-MS: m/z: 614.1 $[M+H]^+$.

2-(*tert*-Butoxyoxalyl-amino)-5-(((5-methoxy-2-methyl-1*H*-indol-3-carbonyl)amino)-methyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.24 g, 0.39 mmol) was dissolved in a 50 % solution of trifluoroacetic acid/dichloromethane (2 ml). The reaction mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo to 1/5 of the volume and the precipitate filtered off. The filtrate was washed with dichloromethane (2x) and dried, which afforded 100 mg (50 %) of the title compound as a solid.

^{1}H-NMR (DMSO-d_6) δ 12.31 (bs, 1H), 10.58 (s, 1H), 7.98 (t, 1H, J = 6.8 Hz), 7.08 (d, 1H, J = 11.2 Hz), 6.98 (d, 1H, J = 2.4 Hz), 6.58 (dd, 1H, J = 11.6 Hz and J = 2.8 Hz), 5.75 (d, 1H, J = 0.8 Hz), 4.77 (d, 1H, J = 19.6 Hz), 4.58 (d, 1H, J = 20 Hz), 3.69 (s, 3H), 3.64-3.62(m, 1H), 3.43 (s, 2H), 3.31-3.20 (m, 1H), 2.92-2.84 (m, 1H), 2.52 (m, 1H-partially obscured by DMSO), 2.30 (s, 3H);

LC-MS: m/z: 500.1 $[M-H]^-$.

EXAMPLE 71



5-(1,3-Dioxo-5-propylcarbamoyl-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid

In a 10-mL scintillating vial, a solution of 2-amino-5-aminomethyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (149 mg, 0.5 mmol) in *N,N*-dimethylformamide (4 mL) was treated with trimellitic anhydride (120 mg, 0.62 mmol) and stirred at 100 °C for 24 hours. The solution was then diluted with ethyl acetate (25 mL) and washed with 0.5N aqueous hydrogen chloride (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo affording 229 mg (100 %) of 2-(2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5*H*-thieno[2,3-

c]pyran-5-ylmethyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.49 (d, 1H, *J* = 9 Hz), 8.00 (d, 1H, *J* = 10 Hz), 4.64-4.54 (m, 2H), 4.08-4.02 (m, 2H), 3.88-3.80 (m, 1H), 2.98-2.83 (m, 1H), 2.68-2.54 (m, 1H), 1.57 (s, 9H).

HPLC (254.4 nm) R_t = 3.98 min.

In a 250 mL round bottom flask, a solution of 2-(2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-5-ylmethyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (500 mg, 1.1 mmol) in dichloromethane (7 mL) was treated with a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (633 mg, 3.2 mmol) in dichloromethane (1.0 mL). After stirring for 4 hours at room temperature the reaction solution was dissolved in ethyl acetate (100 mL) and washed with distilled water (2 x 50 mL), 0.5 N aqueous hydrogen chloride (3 x 50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 370 mg (58 %) of 2-(2-(*tert*-butoxyoxalyl-amino)-3-*tert*-butoxycarbonyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-5-ylmethyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.58 (s, 1H), 8.50 (d, 1H, *J* = 8 Hz), 8.00 (d, 1H, *J* = 8 Hz), 4.84-4.65 (m, 2H), 4.17-4.00 (m, 2H), 3.92-3.84 (m, 1H), 3.08-2.94 (m, 1H), 2.78-2.64 (m, 1H), 1.61 (s, 9H), 1.57 (s, 9H).

In a 50 mL round bottom flask, a solution of 2-(2-(*tert*-butoxyoxalyl-amino)-3-*tert*-butoxycarbonyl-4,7-dihydro-5*H*-thieno[2,3-c]pyran-5-ylmethyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (208 mg, 0.36 mmol) in dichloromethane (5.0 mL) was treated with *N,N*-diisopropyl ethylamine (200 μL, 1.1 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84 mg, 0.44 mmol). The solution was allowed to stir for 50 minutes at room temperature before propylamine (30 μL, 0.36 mmol) was added dropwise. The solution was stirred for an additional 18 hours at room temperature. The volatiles were evaporated in vacuo and the

residue was purified by silica gel chromatography using a mixture of hexane/ethyl acetate (9:1) as eluent, which afforded 51 mg (23 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-5-propylcarbamoyl-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 8.24-8.16 (m, 2H), 7.93 (d, 1H, J = 8 Hz), 6.39 (t, 1H, J = 6 Hz), 4.18-4.63 (m, 2H), 4.10-3.96 (m, 2H), 3.92-3.78 (m, 1H), 3.47 (q, 2H, J = 7 Hz), 2.99 (d, 1H, J = 17), 2.76-2.60 (m, 1H), 1.68 (q, 2H, J = 7 Hz), 1.61 (s, 9H), 1.57 (s, 9H), 1.01 (t, 3H, J = 7 Hz).

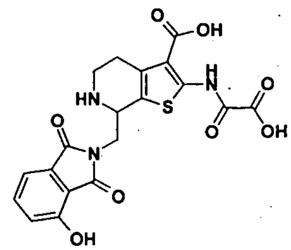
In a 25 mL round bottom flask 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-5-propylcarbamoyl-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (40 mg, 0.07 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (4 mL). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and washed with diethyl ether, affording 32 mg (90 %) of the title compound as a solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ12.32 (s, 1H), 8.81 (s, 1H), 8.58 (s, 1H), 8.00 (s, 1H), 4.90-4.48 (m partially obscured by water, 2H), 4.00-3.64 (m partially obscured by water, 3H), 3.36-3.16 (m partially obscured by water, 2H), 3.13-2.90 (d partially obscured by water, 1H), 2.69-2.53 (m partially obscured by DMSO, 1H), 1.69-1.38 (m, 2H), 1.00-0.74 (m, 3H).

HPLC (254.4 nm) R_t = 3.09 min.

MS (APCI$^-$) m/z: 515.4 [M-H]$^-$.

EXAMPLE 72



7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-(*tert*-Butoxyoxalyl-amino)-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (50 mg, 0.067 mmol) was dissolved in a mixture of ethyl acetate/ethanol (3 mL, 1:1). Palladium on activated carbon (10%, 10 mg) was added and the solution degassed and stirred under hydrogen (1 atm) for 72 hours. The mixture was filtered through celite and the filter cake washed with hot ethyl acetate. The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography (10% ethyl acetate/dichloromethane) to obtain 42 mg (95%) of 2-(*tert*-butoxyoxalyl-amino)-7-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as an oil.

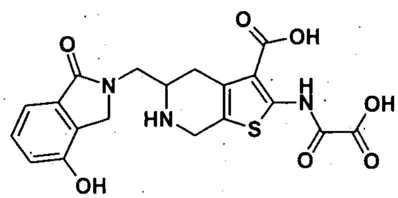
^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.59-12.53 (2s, 1H), 7.64-7.53 (m, 1H), 7.42-7.36 (m, 1H), 7.19-7.11 (m, 1H), 5.58-5.37 (m, 1H), 4.37-4.00 (m, 2H), 3.86-3.78 (m, 1H), 3.32-3.18 (m, 1H), 2.99-2.94 (m, 1H), 2.84-2.69 (m, 1H), 1.62-1.59 (3s, 18H), 1.17-1.11 (2s, 9H);

LC-MS: R_t = 4.55 min, m/z: 658 $[M+H]^+$,

2-(*tert*-Butoxyoxalyl-amino)-7-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (42 mg, 0.064 mmol) was dissolved in a solution of 50% trifluoroacetic acid/methylene chloride (3 mL). The reaction was stirred at ambient temperature for 7 hours, concentrated in vacuo and evaporated from dichloromethane (10 ml) three times. The resulting precipitate was washed with dichloromethane and dried in vacuo to give 29 mg (81 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.32 (bs, 1H), 11.26 (s, 1H), 9.30 (bs, 2H), 7.64 (t, 1H, J = 7 Hz), 7.33 (d, 1H, J = 7 Hz), 7.25 (d, 1H, J = 7 Hz), 4.84 (s, 1H), 4.06-3.96 (m, 2H), 3.56 (m, 2H), 3.05 (bs, 2H), *LC-MS*: R_t = 1.26 min, m/z: $[M+H]^+$,

EXAMPLE 73



5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

Acetyl chloride (5.4 ml, 5.96 g, 76 mmol) was added dropwise to methanol (15 ml) at 0 °C in a sealed 50 ml round-bottom flask. This solution was allowed to warm to room temperature for 1 hour while stirring. To this solution 3-hydroxy-2-methyl-benzoic acid (519 mg, 3.4 mmol) was added and the solution was stirred at room temperature for 42 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and solid sodium bicarbonate. The volatiles were removed in vacuo and the basic aqueous solution was then extracted with dichloromethane (4 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo affording 493 mg (87 %) of 3-hydroxy-2-methyl-benzoic acid methyl ester as a solid.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 1H, J = 9 Hz), 7.12 (t, 1H, J = 8 Hz), 6.95 (d, 1H, J = 8 Hz), 5.05 (bs, 1H), 3.90 (s, 3H), 2.47 (s, 3H).

To a solution of the above methyl ester (256 mg, 1.54 mmol) and N,N-diisopropylethylamine (530 μl, 3.0 mmol) in dichloromethane (8 ml) at 0 °C methyloxymethyl chloride (175 μl, 2.3 mmol) was added dropwise. The solution was allowed slowly to warm to room temperature and stired for 24 hours. The solution was diluted with dichloromethane (12 ml), washed with

water (20 ml), brine (20 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (4:1) as eluent, which afforded 269 mg (85 %) of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, J = 8 Hz), 7.24-7.15 (m, 2H), 5.22 (s, 2H), 3.90 (s, 3H), 3.50 (s, 3H), 2.47 (s, 3H).

In a 25 ml round-bottom flask, *N*-bromosuccinimide (236 mg, 1.3 mmol) and azobis(cyclohexanecarbonitrile) (33 mg, 0.14 mmol) were added to a solution of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester (265 mg, 1.26 mmol) in carbon tetrachloride (6.5 ml). The reaction was heated to reflux with stirring for 3.5 hours. The volatiles were removed in vacuo and the residue purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (9:1) as eluent, which afforded 364 mg (100 %) of 2-bromomethyl-3-methoxymethoxy-benzoic acid methyl ester as a solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, 1H, J = 6,3 Hz), 7.29 (d, 2H, J = 3 Hz), 5.27 (s, 2H), 5.05 (s, 2H), 3.91 (s, 3H), 3.50 (s, 3H).

In a 100 ml round-bottom flask, 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (298 mg, 0.74 mmol) and N,N-diisopropylethylamine (195 μl, 1.12 mmol) were dissolved in acetonitrile (40 ml). 2-Bromomethyl-3-methoxymethoxy-benzoic acid methyl ester (193 mg, 0.67 mmol) in acetonitrile (5 ml) was slowly added to the amine solution via gastight syringe over 24 hours, followed by stirring at room temperature for an additional 36 hours. The solution was concentrated in vacuo, the residue redissolved in ethyl acetate (25 ml), and washed with saturated aqueous sodium bicarbonate (25 ml) and brine (25 ml). The organic phase was dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (1:1) as eluent, which afforded 345 mg (81 %) of 2-amino-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-

ylmethyl)-4,5,6,7-tetrahydro[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.67 (d, 1H, J = 8 Hz), 7.57-7.38 (m, 5H), 7.14 (d, 2H, J = 8 Hz), 6.96 (m, 2H), 6.77 (d, 2H, J = 9 Hz), 6.20 (d, 2H, J = 6 Hz), 5.96 (s, 2H), 4.69-2.58 (m, 17H), 1.55 (s, 9H).

In a 50 ml round-bottom flask a solution of 2-amino-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (338 mg, 0.58 mmol) in dichloromethane (20 ml) was treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (575 mg, 2.9 mmol). After stirring for 18 hours at room temperature, the mixture was concentrated to dryness <u>in</u> <u>vacuo</u>. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (1:1) as eluent, which afforded 310 mg (75 %) of 2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.57 (s, 1H), 7.53 (d, 1H, J = 8 Hz), 7.43 (t, 1H, J = 8 Hz), 7.26 (d, 1H, J = 8 Hz), 7.13 (d, 2H, J = 9 Hz), 6.78 (d, 2H, J = 9 Hz), 5.28 (s, 2H), 4.47 (q, 2H, J = 18 Hz), 4.02-3.44 (m, 11H), 2.97 (dd, 1H, J = 18 Hz and J = 5 Hz), 2.76 (dd, 1H, J = 17 Hz and J = 5 Hz), 1.63 (s, 9H), 1.59 (s, 9H).

10 % Pd/C (145 mg, 50 % by weight) was added to a mixture of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (283 mg, 0.40 mmol) in 10 % formic acid and methanol (10 ml). After stirring at room temperature for 18 hours, more Pd/C (141 mg, 50 % by weight) was added to the reaction mixture. After stirring at room temperature for an additional 20 hours, the catalyst was removed via fitration through celite. Fresh Pd/C (255 mg) and ammonium formate (1.0 g) were added to the residue (253 mg, 0.36 mmol) dissolved in 10 % formic acid in methanol (10 ml). The solution was

heated to 40 °C for 48 hours. Catalyst was removed via filtration through celite and liberal washing with methanol. Purification by chromatotron (ethyl acetate/triethylamine (99:1)) afforded 63 mg (27 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **A** and 46 mg (19 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **B**.

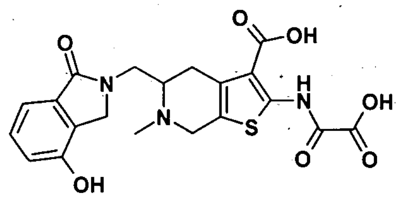
A: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.54 (s, 1H), 7.50 (d, 1H, J = 8 Hz), 7.41 (t, 1H, J = 8 Hz), 7.25 (d, 1H, J = 8 Hz), 5.27 (s, 2H), 4.52 (dd, 2H, J = 30 Hz and J = 19 Hz), 4.08-3.90 (m, 2H), 3.86-3.67 (m, 2H), 3.51 (s, 3H), 3.27 (m, 1H), 2.99 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.53 (dd, 1H, J =18 Hz and J = 11 Hz), 1.61 (s, 9H), 1.53 (s, 9H).
LC-MS (APCI$^+$) m/z: 588 $[M+H]^+$; R_t = 1.32 min.

B: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.56 (s, 1H), 7.50 (d, 1H, J = 7 Hz), 7.41 (t, 1H, J = 8 Hz), 7.25 (d, 1H, J = 8 Hz), 5.27 (s, 2H), 4.50 (dd, J = 28 Hz and J = 18 Hz), 3.93-3.68 (m, 4H), 3.51 (s, 1H), 3.51 (s, 3H), 3.31 (m, 1H), 2.88 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.68 (dd, 1H, J =19 Hz and J = 9 Hz), 2.46 (s, 3H), 1.61 (s, 9H), 1.54 (s, 9H).
LC-MS (APCI$^+$) m/z: 602 $[M+H]^+$; R_t = 1.35 min.

2-(*tert*-Butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **A** (63 mg, 0.11 mmol) was dissolved in 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and washed with diethyl ether, affording 57 mg (90 %) of the title compound as a solid trifluoroacetate.
^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.30 (s, 1H), 10.17 (s, 1H), 9.23 (s, 2H, J = 5 Hz and J = 7 Hz), 7.34 (t, 1H, J = 6 Hz), 7.19 (d, 1H, J = 5 Hz), 7.03 (d, 1H, J = 6 Hz), 5.76 (s, 2H), 4.53 (d, 1H, J = 13 Hz), 4.43-4.22 (m, 3H),

4.07 (m, 1H), 3.91 (m, 1H), 3.70 (m, 1H), 3.10 (m, 1H), 2.82 (dd, 1H, J = 14 Hz and J = 8 Hz).

EXAMPLE 74



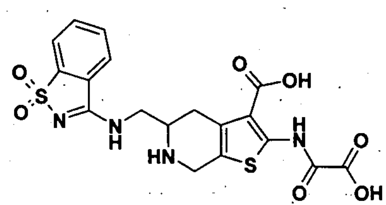
5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **B** (46 mg, 0.08 mmol) was dissolved in 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and washed with diethyl ether, affording 41 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.39 (s, 1H), 10.19 (s, 1H), 10.10 (s, 1H), 7.32 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.02 (t, 1H, J = 7.2 Hz), 4.55 (d, 2H, J = 15 Hz), 4.0-4.5 (m, 4H), 2.95-3.70 (m, 5H), 2.85 (s, 3H).

LC-MS (APCI$^+$) m/z: 446 $[M+H]^+$; R_t = 1.02 min.

EXAMPLE 75



5-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

Saccharin (8.8 g, 48 mmol) and phosphorous pentachloride (15 g, 72 mmol) were added neat to a round bottom flask equipped with a short path distillation column. The mixture was heated to 175 °C. After approximately 0.5 hour, phosphorous oxychloride slowly distilled off. Upon completion of the reaction, the mixture was cooled and the resultant solid recrystallized from benzene affording 3.6 g (37 %) of 3-chloro-benzo[d]isothiazole 1,1-dioxide as a solid.

^{1}H-NMR ($CDCl_3$): δ 7.92 (d, 1H, J = 6.9 Hz), 7.8 (m, 3H).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (155 mg, 0.384 mmol) and triethylamine (59 μl, 0.423 mmol) in dichloromethane (2 ml) at 0 °C, was added a solution of 3-chloro-benzo[d]isothiazole 1,1-dioxide (85.2 mg, 0.423 mmol) in dichloromethane (2 ml). The reaction mixture was stirred at 0 °C for 1hour. The reaction was judged complete by tlc (dichloromethane/ethyl acetate (1:1)). The reaction mixture was washed with water (3 x 20 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The crude residue was subjected to flash chromatography using a gradient from 100 % dichloromethane to dichloromethane/ethyl acetate (80/20) as eluent, which afforded 200 mg (92 %) of 2-amino-5-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a foam.

^{1}H-NMR (CD_3OD): δ 7.99 (m, 1H), 7.87 (m, 1H), 7.79 (m, 2H), 7.19 (d, 2H, J = 8.4 Hz), 6.75 (d, 2H, J = 8.7 Hz), 3.88-3.79 (m, 2H), 3.75-3.59 (m, 3H), 3.69 (s, 3H), 3.52-3.46 (m, 2H), 2.84 (dd, 1H, J = 15.3 Hz and J = 5.4 Hz), 2.68 (dd, J = 18 Hz and J = 4.5 Hz), 1.46 (s, 9H).

LC-MS: R_t = 2.83, m/z: 569 $[M+H]^+$

To a solution of 2-amino-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (129 mg, 0.227 mmol) in tetrahydrofuran (3 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (1.1 ml, 1.1

mmol, 1 M in tetrahydrofuran). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue subjected to flash chromtography using a mixture of ethyl acetate/dichloromethane (10:90) as eluent, which afforded 142 mg (90%) of 2-(*tert*-butoxyoxalyl-amino)-5-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ 7.92 (d, 1H, J = 6.3 Hz), 7.73 (m, 2H), 7.56 (d, 1H, J = 5.7 Hz), 7.20 (d, 2H, J = 6.3 Hz), 7.05 (bs, 1H), 6.87 (d, 2H, J = 6.6 Hz), 3.91 (m, 2H), 3.82-3.72 (m, 2H), 3.79 (s, 3H), 3.61-3.49 (m, 2H), 3.44 (m, 1H), 3.11 (dd, 1H, J = 15 Hz and J = 3.6 Hz), 2.72 (dd, 1H, J = 12 Hz and J = 4.2 Hz), 1.63 (s, 18H);

LC-MS: R_t=3.48, m/z: 697 $[M+H]^+$

2-(*tert*-Butoxyoxalyl-amino)-5-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (120 mg, 0.172 mmol) was dissolved in a mixture of ethanol (4 ml) and formic acid (0.5 ml). 10 % Pd-C (20 mg) was added and the reaction mixture stirred at ambient temperature for 4 days (after the second day, 150 mg of additional 10 % Pd-C was added). The reaction mixture was filtered through celite and the celite washed with dichloromethane. The organic fractions were combined and concentrated <u>in vacuo</u>. The resultant oil was subjected to preparative thin layer chromatography (dichloromethane/methanol (95:5)), which afforded 17 mg (17 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

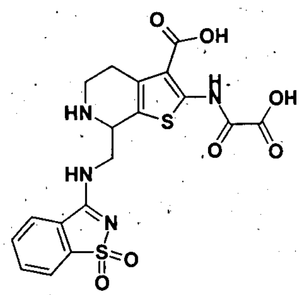
^{1}H-NMR ($CDCl_3$): δ 7.91 (m, 1H), 7.72 (m, 3H), 7.34 (bs, 1H), 4.16-4.08 (m, 1H), 4.07 (dd, 2H, J = 36.3 Hz and J = 8.7 Hz), 3.38-3.30 (m, 1H), 3.22-3.06 (m, 2H), 2.51 (dd, 1H, J = 16.8 Hz and J = 9.9 Hz), 1.61 (s, 18H).

2-(*tert*-Butoxyoxalyl-amino)-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

tert-butyl ester (15 mg, 0.026 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo and re-evaporated from acetonitrile (2x). The residue was washed with dichloromethane and dried in vacuo to give 16 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (CD_3OD): δ 7.98 (d, 1H, J = 7.2 Hz), 7.92 (d, 1H, J = 6.6 Hz), 7.83 (m, 2H), 4.51-4.39 (m, 2H), 4.11-4.08 (m, 1H), 3.97-3.91 (m, 2H), 3.53-3.47 (m, 1H), 3.16-3.10 (m, 1H).

EXAMPLE 76



7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

3-Chloro-benzo[d]isothiazole-1,1-dioxide (160 mg, 0.79 mmol) and diisopropylethylamine (150 μl, 0.86 mmol) were dissolved in dichloromethane (7 ml) at 0 °C. 2-Amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (284 mg, 0.70 mmol) was added and the mixture was stirred for 15 minutes at 0 °C, diluted with dichloromethane (10 ml) and washed with water (20 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of hexanes/ethyl acetate (1:1) to pure ethyl acetate as eluent, which afforded 309 mg (77 %) of 2-amino-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an foam.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, J = 8 Hz), 7.77-7.63 (m, 2H), 7.37 (d, 1H, J = 7 Hz), 7.25 (d, 2H, J = 10 Hz), 6.82 (d, 2H, J = 8 Hz), 6.62 (bs, 1H), 6.08 (s, 2H), 3.91 (m, 1H), 3.71 (s, 3H), 3.49-2.65 (m, 8H), 1.59 (s, 9H).
LC-MS (APCI$^+$) m/z: 569 $[M+H]^+$, [M+Na] 591; R_t = 2.85 min.

2-Amino-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (102 mg, 0.18 mmol) in dichloromethane (10 ml) was treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (85 mg, 0.43 mmol). After stirring for 18 hours at room temperature, the reaction solution was concentrated to dryness <u>in vacuo</u>. The residue was purified by silica gel chromatography using a gradient of hexanes/ethyl acetate (1:1) to pure ethyl acetate as gradient, which afforded 98 mg (78 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.57 (s, 1H), 7.89 (d, 1H, J = 8 Hz), 7.77-7.63 (m, 2H), 7.39 (d, 1H, J = 7 Hz), 7.25 (d, 2H, J = 9 Hz), 6.84 (d, 2H, J = 9 Hz), 6.64 (bs, 1H), 3.99-2.76 (m, 12H), 1.64 (s, 9H), 1.63 (s, 9H).
10 % Pd/C (100 mg) was added to a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (98 mg, 0.14 mmol) in 10 % formic acid in methanol (10 ml). After stirring at room temperature for 48 hours, the catalyst was removed via filtration through celite and liberal washing with methanol. The volatiles were removed <u>in vacuo</u> and the residue purified by chromatotron (ethyl acetate/triethylamine, 99:1), which afforded 32 mg (40 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.48 (s, 1H), 10.21-9.15 (m, 2H), 8.49-7.42 (m, 3H), 5.62-5.00 (bs, 1H), 4.53-2.87 (m, 8H), 1.61 (s, 18H).

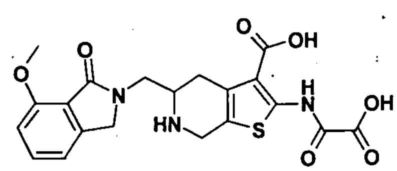
HPLC (254.4 nm) R_t = 3.67 minutes.

2-(*tert*-Butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (32 mg) was dissolved in a mixture of 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and washed with diethyl ether, affording 29 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.36 (s, 1H), 9.92 (bs, 1H), 9.73 (bs, 1H), 9.38 (bs, 1H), 8.20 (m, 1H), 8.05 (m, 1H), 7.89 (m, 2H), 4.95 (s, 1H), 4.12-3.00 (m partially obscured by water, 8H).

LC-MS (APCI$^+$) m/z: 466 [M+H]$^+$; R_t = 0.66 min.

EXAMPLE 77



5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-Methoxy-6-methylbenzoic acid ethyl ester (500 mg, 2.67 mmol), *N*-bromosuccinimide (483.8 mg, 2.72 mmol) and 2,2'-azobis(2-methyl-propionitrile) (30.2 mg, 0.123 mmol) in carbon tetrachloride (10 ml) were heated to reflux. After 18 hours, the reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in dichloromethane (100 ml) and washed with water (2 x 50 ml). The organic layer was dried ($MgSO_4$),

filtered and the solvent evaporated in vacuo. The residue (702 mg) was purified by column chromatography using a mixture of hexanes/dichloromethane (1:1) as eluent, which afforded 573 mg (85 %) of 6-bromomethyl-2-methoxy-benzoic acid ethyl ester as an oil.
^{1}H-NMR ($CDCl_3$): δ 7.37 (t, 1H, J = 8.4 Hz), 7.01 (d, 1H, J = 8.1 Hz), 6.90 (d, 1H, J = 8.4 Hz), 4.54 (s, 2H), 4.45 (q, 2H, J = 7.2 Hz), 3.82 (s, 3H), 1.42 (t, 3H, J = 9 Hz).

6-Bromomethyl-2-methoxy-benzoic acid ethyl ester (71.1 mg, 0.260 mmol) dissolved in acetonitrile (5 ml) and diisopropylethylamine (453 μl, 2.60 mmol) was stirred at room temperature. To this mixture 2-amino-5-amino-methyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (200 mg, 0.52 mmol) dissolved in acetonitrile (5 ml) was added syringe pump (0.2 ml/min.). Once addition was complete, the reaction mixture was allowed to stir for 2 hours. The reaction mixture was concentrated in vacuo, and the residue diluted with ethylacetate (50 ml). The organic layer was washed with saturated sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue (308 mg) was subjected to column chromatography using a gradient of hexane/ethyl acetate (95:5) to (50:50) and then dichloromethane/ethyl acetate (95:5) as eluents, which afforded 106 mg (75 %) of 2-amino-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H-NMR ($CDCl_3$): δ 7.48 (t, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 8.4 Hz), 7.01 (d, 1H, J = 7.5 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.76 (d, 2H, J = 7.8 Hz), 5.95 (bs, 2H), 4.37 (s, 2H), 4.05 (m, 1H), 3.97 (s, 3H), 3.88-3.78 (m, 2H), 3.81 (s, 3H), 3.71-3.39 (m, 4H), 2.90 (dd, 1H, J = 18 Hz and J = 5.4 Hz), 2.62 (dd, 1H, J = 18 Hz and J = 5.4 Hz), 1.53 (s, 9H).

To a solution of 2-amino-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (105 mg, 0.192 mmol) in tetrahydrofuran (3

ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.534 ml, 0.534 mmol, 1 M in tetrahydrofuran). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture concentrated in vacuo and the residue subjected to flash chromtography using a mixture of ethyl acetate/dichloromethane (10:90) as eluent, which afforded 85 mg (66 %) of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR ($CDCl_3$): δ 7.47 (t, 1H, J = 5.7 Hz), 7.10 (d, 2H, J = 6 Hz), 6.99 (d, 1H, J = 5.7 Hz), 6.90 (d, 1H, J = 6.3 Hz), 6.76 (d, 2H, J = 6.3 Hz), 4.37 (q, 2H, J = 11.4 Hz), 3.99-3.92 (m, 1H), 3.97 (s, 3H), 3.79-3.76 (m, 2H), 3.77 (s, 3H), 3.66 (d, 1H, J = 12.6 Hz), 3.58-3.50 (m, 3H), 2.95 (dd, 1H, J = 13.5 Hz and J = 3.6 Hz), 2.70 (dd, 1H, J = 13.5 Hz and J = 3.6 Hz), 1.61 (d, 9H), 1.57 (s, 9H).

2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (66 mg, 0.12 mmol) was dissolved in ethanol (2 ml) and formic acid (0.3 ml). 10 % Pd-C (15 mg) was added and the reaction mixture stirred at room temperature for 3 days. TLC (hexane/ethyl acetate (1/1)) indicated reaction complete. The reaction mixture was filtered through celite and the celite washed with dichloromethane. The organic fractions were combined and subjected to preparative thin layer chromatography (hexane/ethyl acetate (1/1) to yield 14.7 mg (22 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ 7.48 (t, 1H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.2 Hz), 6.90 (d, 1H, J = 8.4 Hz), 5.50 (d, 2H, J = 6.6 Hz), 4.04-3.90 (m, 1H), 3.97 (s, 3H), 3.24 (m, 1H), 3.01-2.95 (m, 1H), 2.57-2.43 (m, 2H), 1.62 (s, 9H), 1.57 (s, 9H).

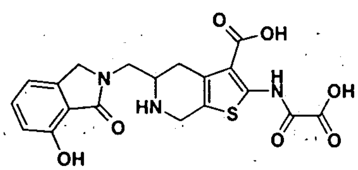
2-(*tert*-Butoxyoxalyl-amino)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-

butyl ester (14.7 mg, 0.026 mmol) was dissolved in a solution of 50% trifluoroacetic acid/dichloromethane (2 ml). The reaction mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo and re-evaporated from acetonitrile (2x). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 13 mg (89 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (CD_3OD): δ 7.56 (t, 1H, J = 8.1 Hz), 7.13 (d, 1H, J = 7.2 Hz), 7.01 (d, 1H, J = 8.1 Hz), 4.87-4.44 (m, 4H), 4.15 (m, 1H), 3.90 (s, 3H), 3.88-3.79 (m, 1H), 3.43 (m, 1H), 2.98 (m, 2H);

LC-MS: R_t = 0.71, m/z: 446 $[M+H]^+$.

EXAMPLE 78



5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-hydroxy-6-methyl-benzoic acid ethyl ester (5.00 g, 27.8 mmol) and t-butyl-di-methylsilyl chloride (6.27 g, 41.6 mmol) in dichloromethane (100 ml) was added diisopropyl ethylamine. The solution was stirred at 50 °C for 24 hours, washed with water, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo, which afforded 7.6 g (93 %) of 2-(*tert*-butyl-dimethyl-silanyloxy)-6-methyl-benzoic acid ethyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ 7.13 (t, 1H, J = 7.5 Hz), 6.78 (d, 1H, J = 7.5 Hz), 6.67 (d, 1H, J = 7.5 Hz), 4.35 (q, 2H, J = 7.2 Hz), 2.29 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz), 0.97 (s, 9H), 0.23 (s, 6H).

2-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-benzoic acid ethyl ester (7.6 g, 25.8 mmol), N-bromosuccinimide (4.82 g, 27.1 mmol) and azobis(cyclohexanecarbonitrile) (0.32 g, 1.3 mmol) were dissolved in

tetrachlormethane (130 ml). The solution was stirred at room temperature for 60 hours. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel column using a gradient of 1-2% ethyl acetate/hexane as eluent, which afforded 8.0 g (83 %) of 6-bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester as an oil. ^{1}H-NMR ($CDCl_3$): δ 7.21 (t, 1H, J = 8.4 Hz), 7.00 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.4 Hz), 4.51 (s, 2H), 4.40 (q, 2H, J = 7.2 Hz), 1.42 (t, 3H, J = 7.2 Hz), 0.98 (s, 9H), 0.23 (s, 6H).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (3.00 g, 7.45 mmol) and diisopropyl ethylamine (1.93 ml, 11.2 mmol) in acetonitrile at room temperature was added a solution of 6-bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester (2.78 g, 7.45 mmol) in acetonitril over 48 hours. The solution was stirred for 12 hours after the addition was complete. The volatiles were evaporated in vacuo and the residue was taken into ethyl acetate (50 ml) and washed with water, 1 N hydrochloric acid, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column eluted with a mixture of 20 % ethyl acetate/Hexane, which afforded 3.2 g (66 %) of 2-amino-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl]-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil. ^{1}H-NMR ($CDCl_3$): δ 7.36 (t, 1H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.8 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 6.76 (d, 2H, J = 8.8 Hz), 5.94 (s, 2H), 4.48 (d, 1H, J = 16.8 Hz), 4.33 (d, 1H, J = 16.8 Hz), 3.90-3.45 (m, 7H), 3.78 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 2.72 (dd, 1H, J = 17 Hz and J = 5.6 Hz), 1.52 (s, 9H), 1.05 (s, 9H), 0.26 (s, 6H).

To a stirred solution of 2-amino-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.37 g, 3.64 mmol) in tetrahydrofuran (50 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-

butyl ester (2.14 mg, 10.9 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (100 ml). The solution was washed with 0.5 N hydrochloric acid solution (2 x 20 ml), saturated sodium bicarbonate (2 x 20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was chromatographed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 2.40 g (92 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR ($CDCl_3$): δ 12.59 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.77 (d, 2H, J = 8.8 Hz), 4.50 (d, 1H, J = 16.8 Hz), 4.34 (d, 1H, J = 16.8 Hz), 3.90-3.45 (m, 7H), 3.77 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 2.72 (dd, 1H, J = 18 and J = 5.6 Hz), 1.61 (s, 9H), 1.58 (s, 9H), 1.06 (s, 9H), 0.26 (s, 6H).

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.40 g, 3.34 mmol) in 10 % formic acid/methanol (50 ml) at room temperature under nitrogen was added 10 % Pd/C (1.2 g). The mixture was stirred for 48 hours. The Pd/C was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane (10 ml). The resulting solution was poured into hexane. The precipitate was filtered off and dried in vacuo affording 1.3 g (61 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR ($CDCl_3$): δ 12.45 (s, 1H), 8.05 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.00 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 4.50 (d, 1H, J = 16.8 Hz), 4.45 (q, 2H, J = 17 Hz), 4.05 (q, 2H, J = 17 Hz), 3.82 (dd, 1H, J =

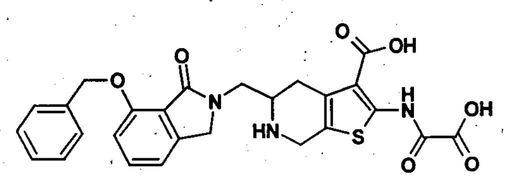
17.2 Hz and J = 5.2 Hz), 3.72 (dd, 1H, J = 17 Hz and J = 5.6 Hz), 3.40 (s, 1H), 3.08 (d, 1H, J = 17 Hz), 2.61 (dd, 1H, J = 18 Hz and J = 7.2 Hz), 1.61 (s, 9H), 1.54 (s, 9H), 1.05 (s, 9H), 0.26 (s, 6H).

To a solution of trifluoroacetic acid (33.3 ml) and H_2O (2.7 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.70 g, 1.04 mmol). The solution was stirred at room temperature for 40 hours. The solvent was poured into ethyl ether (400 ml). The precipitate was filtered off and dried in vacuo, which afforded 450 mg (80 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.30 (s, 1H), 9.71 (s, 1H), 9.20 (s, 2H), 7.39 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 4.52 (d, 1H, J = 16.8 Hz), 4.36 (d, 2H, J = 17 Hz), 4.22 (d, 2H, J = 17 Hz), 4.00 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.86 (s, 1H), 3.62 (d, 1H, J = 17 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz);

LC-MS: R_t = 1.20 min; m/z = 432 $[M+H]^+$

EXAMPLE 79



5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.40 g, 3.34 mmol) in 10 % formic acid/methanol (50 ml) at room temperature under nitrogen was added 10 % Pd/C (1.2 g). The mixture was stirred for 48 hours. The Pd/C was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane (10 ml) and the resulting solution was poured into hexane. The precipitate was

filtered off (1.3 g) and the filtrate was evaporated in vacuo. The residual foam (1.1 g) was taken into dichloromethane (50 ml) and treated with di-*tert*-butyl-dicarbonate (1.1 g, 5.0 mmol) and saturated sodium bicarbonate (20 ml). The mixture was stirred for 2 hours and the organic layer was separated and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was chromatographed using a gradient of 10-30% ethyl acetate/Hexane as eluent, which afforded 175 mg of 2-(*tert*-butoxyoxalyl-amino)-5-(7-hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester.

^{1}H-NMR ($CDCl_3$): δ 12.55 (s, 1H), 8.53 (s, 1H), 7.37 (t, 1H, J = 7.6 Hz), 6.92 (d, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.6 Hz), 4.95 (s, 1H), 4.84 (d, 1H, J = 16.4 Hz), 4.72 (d, 1H, J = 16.0 Hz), 4.56 (d, 1H, J = 16.0 Hz), 4.28 (d, 1H, J = 17.6 Hz), 4.13 (m, 1H), 3.68 (s, 0.5H), 3.42 (s, 0.5H), 3.16-2.94 (m, 2H), 1.62 (s, 9H), 1.61 (s, 9H), 1.26 (s, 9H).

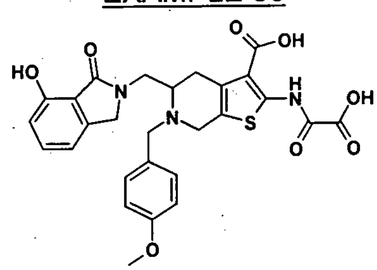
To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(7-hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester (16 mg, 0.025 mmol) in N,N-dimethylformamide (0.5 ml) under nitrogen was added sodium hydride (1.0 mg, 0.026 mmol) at room temperature. The solution was stirred for 2 hours and followed by addition of benzyl bromide (5.9 ml, 0.050 mmol). The solution was stirred for 16 hours, diluted with ethyl acetate (20 ml) and washed with 0.5 N hydrochloric acid solution (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml), brine (10 ml), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo. The residue was chromatographed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 14 mg (76 %) of 5-(7-benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester as a solid.

^{1}H-NMR ($CDCl_3$): δ 12.49 (s, 1H), 7.48 (d, 2H, J = 7.2 Hz), 7.35 (m, 3H), 7.28 (d, 1H, J = 7.2 Hz), 6.97 (d, 1H, J = 7.6 Hz), 6.80 (d, 1H, J = 7.6 Hz), 5.32 (s, 2H), 4.97 (m, 2H), 4.82-4.62 (m, 2H), 4.45-4.15 (m, 2H), 3.68 (s,

0.5H), 3.48 (s, 0.5H), 3.16-2.94 (m, 2H), 1.62 (s, 9H), 1.60 (s, 9H), 1.26 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (2.7 ml) was added 5-(7-benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester (14 mg, 0.019 mmol). The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate was filtered off and dried in vacuo affording 8.0 mg (68 %) of the title compound as a solid trifluoroacetate. ^{1}H-NMR (DMSO-d_6): δ 12.25 (s, 1H), 9.28 (s, 1H), 9.02 (s, 1H), 7.53 (m, 3H), 7.39 (t, 2H, J = 7.6 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 8.4 Hz), 5.27 (m, 2H), 4.54 (d, 1H, J = 17.2 Hz), 4.38 (d, 2H, J = 17.6 Hz), 4.22 (m, 2H), 4.00 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.86 (s, 1H), 3.64 (d, 1H, J = 17.2 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz);
LC-MS: R_t = 2.96 min; m/z: 522 $[M+H]^+$

EXAMPLE 80



5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

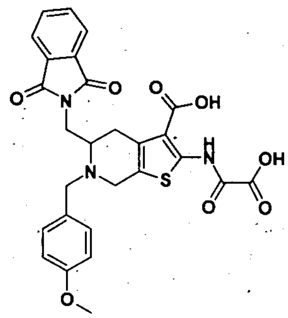
To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (11 mg, 0.014 mmol). The solution was stirred at room temperature for 16 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate

was filtered off and dried in vacuo, which afforded 7.0 mg (79 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.39 (s, 1H), 9.95 (s, 1H), 9.75 (s, 2H), 7.42 (t, 1H, J = 8.0 Hz), 7.30 (s, 2H), 7.02 (d, 1H, J = 7.2 Hz), 6.96 (s, 2H), 6.85 (d, 1H, J = 7.2 Hz), 4.95-3.65 (m, 11H), 3.76 (s, 3H).

LC-MS: R_t = 1.93 min, m/z: 553 [M+H]$^+$

EXAMPLE 81



5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a stirred solution of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (15 mg, 0.028 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (27 mg, 0.11 mmol) in tetrahydrofuran (1.0 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (20 ml). The solution was washed with 0.5 N hydrochloric acid solution (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml) and brine (10 ml), dried ($MgSO_4$) and filtered. The solvent was removed in vacuo. The residue was chromatographed using a gradient of 10-25 % ethyl acetate/hexane as eluent, which afforded 17 mg (93 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

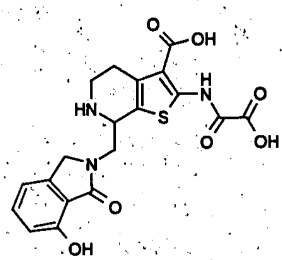
^{1}H-NMR ($CDCl_3$): δ 12.54 (s, 1H), 7.86 (m, 2H), 7.40 (m, 2H), 7.08 (d, 2H, J = 8.4 Hz), 6.72 (d, 2H, J = 8.4 Hz), 4.08 (dd, 1H, J = 13.6 Hz and J = 8.8 Hz), 3.94 (d, 1H, J = 16.8 Hz), 3.82 (d, 1H, J = 12.8 Hz), 3.78 (s, 3H), 3.92 (s, 3H), 3.70-3.56 (m, 3H), 3.53 (d, 1H, J = 12.8), 2.93 (dd, 1H, J = 16.8 Hz and J = 4.8 Hz), 2.75 (dd, 1H, J = 18.0 Hz and J = 5.6 Hz), 1.61 (s, 9H), 1.58 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (15 mg, 0.023 mmol). The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate was filtered off and dried <u>in vacuo</u>, which afforded 13 mg (87 %) of the <u>title compound</u> as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.38 (s, 1H), 7.89 (d, 4H, J = 11.2 Hz), 7.18 (s, 2H), 6.85 (s, 2H), 4.20-3.60 (m, 9H), 3.71 (s, 3H);

LC-MS: R_t = 2.05 min, m/z: 550 $[M+H]^+$

EXAMPLE 82



<u>7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid</u>

To a solution of 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (80 mg, 0.20 mmol) and diisopropyl ethylamine (35 μl, 0.40 mmol) in acetonitrile (10 ml) at room temperature was added a solution of 6-bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester (69 mg, 0.20

mmol). The solution was stirred for 12 hours at room temperature and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (50 ml) and washed with water, 1 N hydrochloric acid, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column eluted with 20 % ethyl acetate/hexane to yield 42 mg (33 %) of 2-amino-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ 7.64 (d, 1H, J = 8.8 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.10-6.80 (m, 5H), 6.09 (s, 2H), 5.0-4.2 (m, 4H), 3.80 (s, 3H), 3.66-2.92 (m, 3H), 1.55 (s, 9H), 1.04 (s, 9H), 0.22 (s, 6H).

To a stirred solution of 2-amino-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (40 mg, 0.060 mmol) in tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (59 mg, 0.30 mmol) in tetrahydrofuran (1 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (20 ml) and the solution was washed with 0.5 N hydrochloric acid (2 x 20 ml), saturated sodium bicarbonate (2 x 20 ml), brine (20 ml), dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the residue was chromatographed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 40 mg (83 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR ($CDCl_3$): δ 12.52 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.94 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.54 (d, 1H, J = 8.4 Hz), 4.26 (d, 1H, J = 16.8 Hz), 3.93-3.84 (m, 2H), 3.77 (d, 1H, J = 16.8 Hz), 3.69 (s, 3H), 3.66-3.48 (m, 3H), 3.42-3.32 (m, 1H), 2.95 (dd, 1H, J = 14.4 Hz and J = 4.8 Hz), 2.92-2.82 (m, 1H), 2.73 (dd, 1H, J = 14.4 Hz and

J = 4.8 Hz), 1.60 (s, 9H), 1.59 (s, 9H), 1.02 (s, 9H), 0.22 (d, 6H, J = 1.6 Hz).

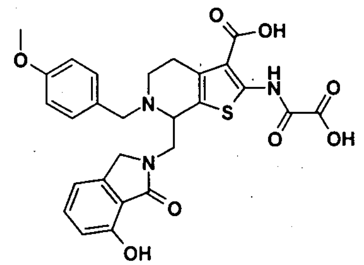
To a solution of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (4.0 mg, 5.1 μmol) in 10 % formic acid/methanol (1 ml) at room temperature under nitrogen was added 10 % Pd/C (4 mg). The mixture was stirred for 1 hour. The Pd/C was filtered off and the filtrate was evaporated in vacuo to afford 2.8 mg (82 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5H-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR ($CDCl_3$): δ 12.45 (s, 1H), 8.05 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.79 (d, 1H, J = 8.0 Hz), 4.50 (d, 1H, J = 17.2 Hz), 4.45 (d, 1H, J = 17.2 Hz), 4.24 (d, 1H, 8.4 Hz), 4.03 (dd, 1H, J = 16.0 Hz and J = 7.2 Hz), 3.78-3.68 (m, 2H), 3.38-3.28 (m, 1H), 3.21 (d, 1H, J = 18.8 Hz), 3.08-2.98 (m, 1H), 1.57 (s, 9H), 1.56 (s, 9H), 0.98 (s, 9H), 0.15 (d, 6H, J = 1 Hz).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5*H*-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.8 mg, 0.0042 mmol). The solution was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was washed with dichloromethane affording 1.8 mg (79 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.30 (s, 1H), 9.76 (s, 1H), 9.40 (s, 1H), 8.95 (s, 1H), 7.40 (t, 1H, J = 7.6 Hz), 7.00 (d, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.6 Hz), 4.92 (s, 1H), 4.54 (d, 1H, J = 18.4 Hz), 4.40 (d, 2H, J = 18.4 Hz), 4.08-4.00 (m, 1H), 3.91 (d, 1H, J = 15.2 Hz), 3.60 (s, 2H), 3.06 (s, 2H); LC-MS: R_t: 1.41 min, m/z: 432 $[M+H]^+$

EXAMPLE 83



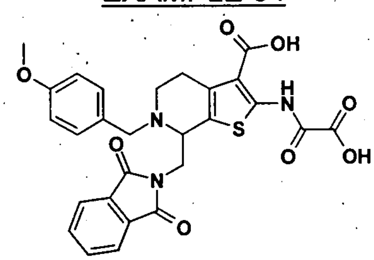
7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (10 mg, 0.013 mmol). The solution was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was washed with dichloromethane, which afforded 6.8 mg (92 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.35 (s, 1H), 9.90 (s, 1H), 9.70 (s, 2H), 7.41 (t, 1H, J = 8.0 Hz), 7.28 (s, 2H), 7.04 (d, 1H, J = 7.2 Hz), 6.92 (s, 2H), 6.83 (d, 1H, J = 7.2 Hz), 4.90-3.60 (m, 11H), 3.80 (s, 3H).

LC-MS: R_t = 1.92 min, m/z: 552 $[M+H]^+$

EXAMPLE 84



7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a stirred solution of 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-

carboxylic acid *tert*-butyl ester (10 mg, 0.019 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (18 mg, 0.092 mmol) in tetrahydrofuran (1.0 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (20 ml) and washed with 0.5 N hydrochloric acid solution (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml), brine (10 ml), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo and the residue was chromatographed using a gradient of 10-25 % ethyl acetate/hexane as eluent, which afforded 11 mg (89 %) of 2-(*tert*-butoxyoxalyl-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

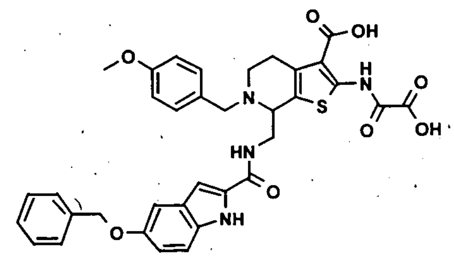
^{1}H-NMR ($CDCl_3$): δ 12.54 (s, 1H), 7.76 (m, 4H), 6.82 (d, 2H, J = 11.6 Hz), 6.33 (d, 2H, J = 11.6 Hz), 4.02 (d, 1H, J = 14.4 Hz), 3.98 (d, 1H, J = 14.4 Hz), 3.62 (s, 3H), 3.62-3.54 (m, 2H), 3.48-3.34 (m, 2H), 3.02-2.70 (m, 3H), 1.60 (s, 9H), 1.59 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (10 mg, 0.015 mmol). The solution was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was washed with dichloromethane, which afforded 6.8 mg (80 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6): δ 12.38 (s, 1H), 7.86 (m, 4H), 6.82 (s, 2H), 6.30 (s, 2H), 4.00-2.86 (m, 9H), 3.58 (s, 3H);

LC-MS: R_t = 2.02 min; m/z: 550 $[M+H]^+$

EXAMPLE 85



7-(((5-Benzyloxy-1*H*-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-Amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (0.50 g; 1.2 mmol) was dissolved in *N,N*-dimethylformamide (20 ml). 1-Hydroxy-7-azabenzotriazole (0.19 g; 1.3 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.26 g; 1.3 mmol) and diisopropylethylamine (0.23 ml; 1.3 mmol) were added and the mixture was stirred for 15 min. 5-Benzyloxyindole (0.36 g; 1.3 mmol) was dissolved in *N,N*-dimethylformamide (20 ml) and added. Diisopropylethylamine (0.23 ml; 1.3 mmol) was added and the mixture was stirred overnight. The solvent was removed in vacuo, the residue dissolved in dichloromethane (30 ml) and the organic phase washed with an aqueous solution of sodium hydrogencarbonate (15 ml). The organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was chromatographed on silica using ethyl acetate/heptane (1:1) as eluent affording 569 mg of 2-amino-7-(((5-benzyloxy-1*H*-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

The title compound was prepared in a similar way as described in Example 48 using the last two steps.

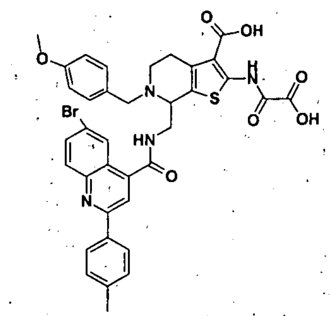
MS: m/z: 669.4 $[M+H]^+$

Calculated for $C_{35}H_{32}N_4O_8S$, 2/3x$C_2HF_3O_2$, 4/3xH_2O ;

C, 56.77%; H, 4.63%; N, 7.29%. Found:

C, 56.43%; H, 4.57%; N, 7.13%.

EXAMPLE 86



7-(((6-Bromo-2-p-tolyl-quinoline-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)- 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acidThe title compound was prepared in a similar way as in Example 84 using 6-bromo-2-p-tolyl-quinoline-4-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

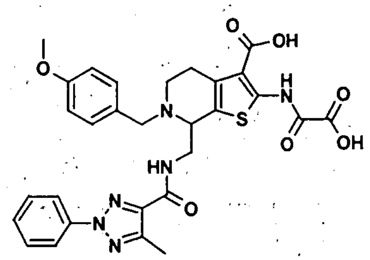
LC-MS: m/z: 745.2 $[M+H]^+$

Calculated for $C_{36}H_{31}BrN_4O_7S$, $2xC_2HF_3O_2$;

C, 49.44%; H, 3.42%; N, 5.77%. Found:

C, 49.19%; H, 3.59%; N, 6.00%.

EXAMPLE 87



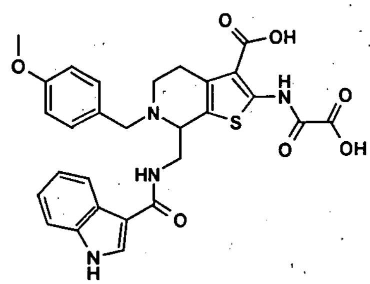
6-(4-Methoxy-benzyl)-7-(((5-methyl-2-phenyl-2*H*-[1,2,3]triazole-4-carbonyl)amino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 5-methyl-2-phenyl-2*H*-[1,2,3]triazole-4-carboxylic acid and 2-amino-7-

aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 605.2 $[M+H]^+$
Calculated for $C_{29}H_{28}N_6O_7S$, 1.3x$C_2HF_3O_2$, 1.7xH_2O;
C, 48.14%; H, 3.94%; N, 10.94%. Found:
C, 48.35%; H, 4.19%; N, 10.68%.

EXAMPLE 88

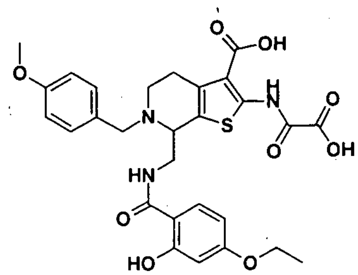


7-(((1*H*-Indole-3-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 3-indole-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 563.2 $[M+H]^+$
Calculated for $C_{28}H_{26}N_4O_7S$, 5/3x$C_2HF_3O_2$;
C, 49.63%; H, 3.82%; N, 7.35%. Found:
C, 50.00%; H, 3.71%; N, 7.44%.

EXAMPLE 89



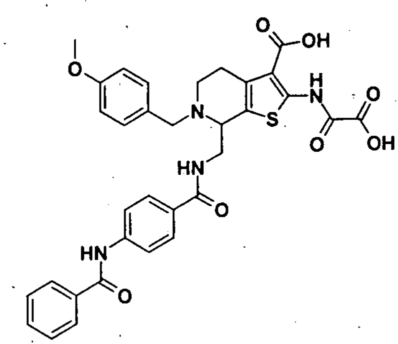
7-((4-Ethoxy-2-hydroxy-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 4-ethoxy-2-hydroxy-benzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 584 $[M+H]^+$

HPLC: (B6): 23.8 min.

EXAMPLE 90



7-((4-Benzoylamino-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 4-benzoylaminobenzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-

benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

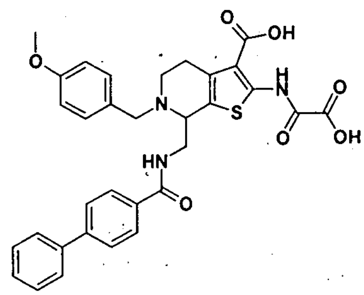
LC-MS: m/z: 643.1 $[M+H]^+$

Calculated for $C_{33}H_{30}N_4O_8S$, $3xC_2HF_3O_2$;

C, 47.57%; H, 3.38%; N, 5.69%. Found:

C, 47.34%; H, 3.55%; N, 5.62%.

EXAMPLE 91



7-(((Biphenyl-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 4-phenylbenzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

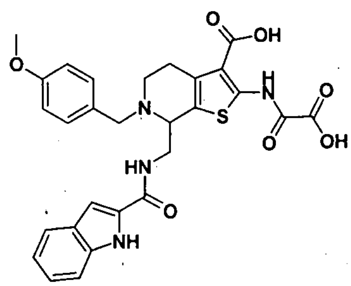
LC-MS: m/z: 599.0 $[M+H]^+$

Calculated for $C_{32}H_{29}N_3O_7S$, $2xC_2HF_3O_2$, $1xH_2O$;

C, 51.13%; H, 3.93%; N, 4.97%. Found:

C, 52.02%; H, 4.02%; N, 5.16%.

EXAMPLE 92



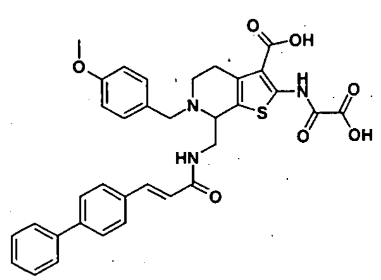
7-(((1*H*-Indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using indole-2-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 563.2 $[M+H]^+$

HPLC (B6) R_t = 23.07 min.

EXAMPLE 93



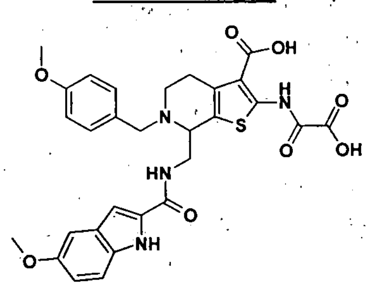
7-((3-Biphenyl-4-yl-acryloylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c)pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 3-biphenyl-4-yl-acrylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 626.2 $[M+H]^+$
HPLC (B6) R_t = 28.74 min.

Calculated for $C_{34}H_{31}N_3O_7S$, $2xC_2HF_3O_2$;
C, 53.46%; H, 3.90%; N, 4.92%. Found:
C, 53.89%; H, 4.23%; N, 5.08%.

EXAMPLE 94

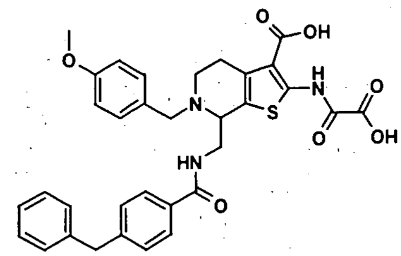


6-(4-Methoxy-benzyl)-7-(((5-methoxy-1*H*-indole-2-carbonyl)amino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 5-methoxyindole-2-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 593.2 $[M+H]^+$
HPLC (B6) R_t = 21.81 min.

EXAMPLE 95



7-((4-Benzyl-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 4-benzylbenzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 614.2 $[M+H]^+$

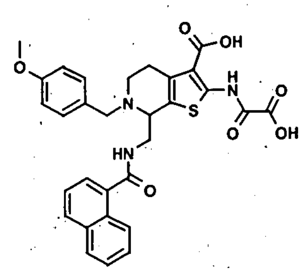
HPLC (B6) R_t = 27.23 min.

Calculated for $C_{33}H_{31}N_3O_7S$, $1.5xC_2HF_3O_2$, $1xH_2O$;

C, 53.87%; H, 4.33%; N, 5.23%. Found:

C, 53.92%; H, 4.24%; N, 5.18%.

EXAMPLE 95



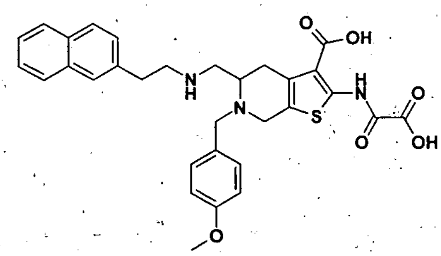
6-(4-Methoxy-benzyl)-7-(((naphthalene-1-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 84 using 1-napthylcarboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

LC-MS: m/z: 574.0 $[M+H]^+$
HPLC (B6) R_t = 22.51 min.

Calculated for $C_{30}H_{27}N_3O_7S$, $2xC_2HF_3O_2$;
C, 50.94%; H, 3.65%; N, 5.24%. Found:
C, 51.39%; H, 3.79%; N, 5.16%.

EXAMPLE 96



6-(4-Methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 2-naphthalen-2-yl-ethanol (1.02 g, 5.8 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (9 mg, 0.058 mmol) and sodium bromide (0.65 g, 6.4 mmol) in a mixture of toluene (18 mL), ethyl acetate (18 mL), and water (3mL) was cooled to 0 °C and added dropwise over 1 hour a solution containing the following: sodium hypochlorite (17.2 mL, 0.37 M, 6.4 mmol) and sodium hydrogencarbonate (1.46 g, 17.4 mmol). The reaction mixture was stirred at 0 °C for 10 min., and the phases separated. The aqueous layer was extracted with ethyl acetate (150 mL). The combined organic phases were washed with a solution of potassium iodone (0.2 g) in 10 % aqueous potassium hydrogensulfate (150 mL),

water (150 mL), brine (150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 980 mg of a 3:1 mixture of naphthalen-2-yl-acetaldehyde and 2-naphthalen-2-yl-ethanol.
^{1}H-NMR ($CDCl_3$): δ 9.81 (t, 1H, J = 1.5 Hz), 7.92-7.80 (*m*, 3H), 7.68 (bs, 1H), 7.55-7.42 (*m*, 3H), 3.87 (d, 2H, J = 1.5 Hz).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (290 mg, 0.71 mmol) in 1,2-dichloroethane (3 ml) was added the above mixture of 2-naphthyl-acetaldehyde (100 mg, 0.59 mmol), sodium triacetoxyborohydride (190 mg, 0.88 mmol) and the mixture was stirred at room temperature under nitrogen for 2.5 hours. The crude reaction mixture was quenched with saturated sodium bicarbonate (50 ml) and the solution extracted with ethyl acetate (100 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo providing a foam, which was taken directly to the next step. LC-MS showed that 2-amino-6-(4-methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component.
LC-MS: m/z: 558.1 $[M+H]^+$, R_f = 2.23 min.

To a solution of 2-amino-6-(4-methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester in tetrahydrofuran (3 ml) was added di-*tert*-butyl-dicarbonate (188 mg, 0.85 mmol) and *N,N*-dimethylformamide (18 mg, 0.14 mmol). The reaction was stirred at room temperature for 7 hours under nitrogen. The crude reaction mixture was diluted with dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo affording a foam, which was used without further purification in the next step.

LC-MS showed that 2-amino-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component. R_f= 2.74, m/z: 658.1 $[M+H]^+$, Calculated: 657.4.

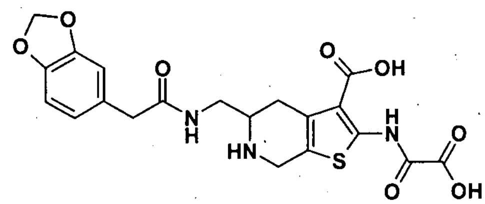
To crude 2-amino-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was added dichloromethane (5 ml) and imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (400 mg, 1.78 mmol) and the reaction mixture stirred at room temperature for 12 hours. The crude reaction mixture was added to dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography using a mixture of dichloromethane/ethyl acetate (10:1) as eluent, which afforded 20.3 mg (39 % over tree steps) of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a foam.
^{1}H NMR ($CDCl_3$) δ 7.99-7.92 (m, 3H), 7.88 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J = 7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 5H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H), 1.79 (s, 9H), 1.71 (s, 18H); LC-MS: m/z: 786.2 $[M+H]^+$, R_f = 3.03 min.

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (20 mg, 0.03 mmol) in dry dichloromethane (200 μl) at 0 °C was added 50 % trifluoroacetic acid in dichloromethane (2.5 ml). The reaction was stirred for 14 hours at room temperature and then concentrated in vacuo. The resultant solid was re-suspended in dichloromethane, filtered, and dried in vacuo to provide 13 mg (90 %) of the title compound as a solid.
^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.09-8.01 (m, 3H), 7.93 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J =7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 4.18-4.12

(m, 2H), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 3H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H);

LC-MS: m/z: 574.7 $[M+H]^+$, R_f = 1.36 min.

EXAMPLE 97



5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a mixture of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (300 mg, 0.74 mmol), benzo[1,3]dioxol-5-yl-acetic acid (134 mg, 0.74 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N,N*-diisopropylethylamine (258 μL, 1.48 mmol) in acetonitrile (5 ml) at room temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol). The reaction mixture was stirred for 16 hours and the solvent evaporated in vacuo. The residue was taken into ethylacetate (50 ml), washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to flash chromatography using a gradient of 10-20% ethylacetate/hexanes as eluent, which afforded 268 mg (64 %) of 2-amino-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 6.95 (bs, 2H), 6.75-6.85 (m, 5H), 5.96 (bs, 2H), 5.95 (s, 2H), 3.81 (s, 3H), 3.75-3.30 (m, 5H), 3.53 (s, 2H), 3.18 (bs, 2H), 2.82 (d, 1H, J = 17 Hz), 2.52 (d, 1H, J = 17 Hz).

To a solution of 2-amino-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (133 mg, 0.235 mmol) in tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (100 mg, 0.51 mmol). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (50 ml) washed with saturated sodium bicarbonate, brine, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was chromatographed using a gradient of 10-20% ethyl acetate/dichloromethane, which afforded 130 mg (80 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

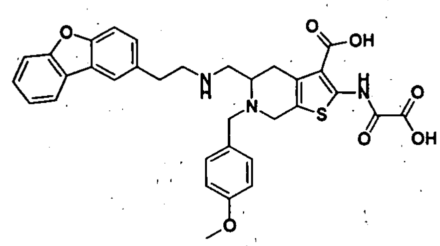
^{1}H-NMR ($CDCl_3$) δ 12.50 (s, 1H), 7.95-7.75 (m, 7H), 5.96 (s, 2H), 3.81 (s, 3H), 3.80-3.40 (m, 5H), 3.15 (bs, 2H), 2.90 (d, 1H, J = 17 Hz), 2.58 (d, 1H, J = 17 Hz), 1.61 (s, 9H), 1.60 (s, 9H).

A solution of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (130 mg, 0.188 mmol) in tetrahydrofuran (2 ml) was passed through a Raney Ni bed (120 mg, 50% Raney Ni-water washed with methanol (6 ml) and tetrahydrofuran (6 ml) and dried before use). The Raney Ni bed was washed with tetrahydrofuran (10 ml). The filtrate and washes were combined and the solvent evaporated in vacuo. The residue was dissolved in 10% formic acid/methanol (6 ml) and stirred with 10% Pd/C (120 mg) for 13 hours. Saturated sodium bicarbonate solution (60 ml) was added to the solution. The mixture was extracted with dichloromethane. The extracts were combined, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was washed with 50% hexane/diethyl ether to afford 62 mg (57 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 12.59 (s, 1H), 6.80-6.70 (m, 3H), 5.96 (s, 2H), 4.05 (q, 2H, J = 15 Hz), 3.85-3.60 (m, 2H), 3.25-3.00 (m, 4H), 2.58 (m, 1H), 1.61 (s, 9H), 1.59 (s, 9H);
LC-MS: R_t = 1.75 min, m/z: 574 $[M+H]^+$.

A solution of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (62 mg, 0.11 mmol) in 50% trifluoroacetic acid-dichloromethane (2 ml) was left in an open flask over the weekend and then the solvent was removed in vacuo. The residue was washed with dichloromethane and the solid filtered off affording 39 mg (62 %) of the title compounds as a solid trifluoroacetate.
^{1}H-NMR (DMSO-d_6) δ 12.39 (s, 1H), 9.18 (bs, 1H), 9.10 (bs, 1H), 8.35 (s, 1H), 6.83 (d, 1H, J = 1.2 Hz), 6.82 (d, 1H, J = 8.4 Hz), 6.70 (dd, 1H, J = 8.4 Hz and J = 1.2 Hz), 5.96 (s, 2H), 4.38 (d, 1H, J = 14 Hz), 4.28 (m, 1H), 3.60-3.40 (m, 4H), 3.16 (d, 2H, J = 14 Hz), 2.80 (dd, 1H, J = 14 Hz and J = 11 Hz);
LC-MS: R_t = 1.11 min, m/z: 462 $[M+H]^+$.

EXAMPLE 98



5-((2-Dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-dibenzofuran-2-yl-ethanol (200 mg, 0.94 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (2 mg, 0.009 mmol) in dichloromethane (2 mL) was added an aqueous solution of sodium bromide (97 mg in 1.3 mL of water for a 0.7M solution, 0.94mmol) and cooled to 0 °C. To this mixture was added dropwise over 30 min., a

solution containing the following: sodium hypochlorite (1.4 mL, 0.74 M, 1.03 mmol) and sodium hydrogencarbonate (120 mg, 1.4 mmol) and water (1.4 mL). The reaction mixture was stirred at 0 °C for 0.5 hour and allowed to warm to room temperature. The organic phase and aqueous layer were separated and the aqueous layer extracted with dichloromethane (20 mL). The combined organic phases were washed with a solution of potassium iodone (0.2 g) in 10% aq. Potassium hydrogensulfate (20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) filtered, and concentrated in vacuo to provide 198 mg of a 5:1 mixture of dibenzofuran-2-yl-acetaldehyde and 2-dibenzofuran-2-yl-ethanol as an oil. ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J = 1.5 Hz), 8.02 (d, 2H, J = 8.2 Hz), 7.71 (bs, 1H), 7.75-7.42 (m, 4H), 3.82 (d, 2H, J = 1.5 Hz).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (340 mg, 0.85 mmol) in 1,2-dichloroethane (3 ml) was added the above mixture of dibenzofuran-2-yl-acetaldehyde (150 mg, 0.70 mmol), and sodium triacetoxyborohydride (225 mg, 1.07 mmol) and the mixture was stirred at room temperature under nitrogen for 2.5 hours. The crude reaction mixture was quenched with saturated sodium bicarbonate (50 ml) and the solution extracted with ethylacetate (100 ml). The organic phase dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The crude residue was taken directly to the next step. LC-MS showed that 2-amino-5-((2-dibenzofuran-2-yl-ethylamino)methyl]-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component in the crude mixture: m/z: 598.1 $[M+H]^+$, R_f = 2.40 min).

Crude 2-amino-5-((2-dibenzofuran-2-yl-ethylamino)methyl]-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was diluted in tetrahydrofuran (3 ml) and di-*tert*-butyl dicarbonate (262 mg, 1.20 mmol) and 4-(*N,N*-dimethylamino)pyridine (25 mg, 0.20 mmol) were added. The reaction was stirred at room temperature for 7 hours under nitrogen. The crude reaction mixture was added to

dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was used directly in the next step. LC-MS showed that 2-amino-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component in the crude: R_f = 2.76, m/z: 698.2 $[M+H]^+$.

To compound 2-amino-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was added dichloromethane (5ml) and imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (420 mg, 2.12 mmol). The reaction mixture was stirred at room temperature for 12 hours. The crude reaction mixture was added to dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was subjected to flash chromatography using a mixture of dichloromethane/ethyl acetate (10:1) as eluent, which afforded 35.2 mg (51 % over 3 steps) of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a foam.
^{1}H-NMR ($CDCl_3$) δ 7.95-7.90 (m, 3H), 7.84 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J = 7.8 Hz), 6.95 (m, 3H), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 5H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H), 1.79 (s, 9H), 1.71 (s, 18H);
LC-MS: R_f = 3.03 min, m/z: 826.2 $[M+H]^+$.

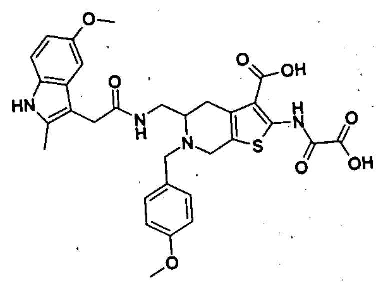
To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (28 mg, 0.034 mmol) in dry dichloromethane (200 μL) at 0 °C was added 50% trifluoroacetic acid in dichloromethane (2.5 ml). The reaction was stirred for 14 hours at room temperature and then concentrated in vacuo. The resultant solid was re-suspended in dichloromethane, filtered, and dried in

vacuo, which afforded 22 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.11-8.21 (m, 3H), 7.93 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J = 7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 4.18-4.12 (m, 2H), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 3H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H);

LC-MS: R_f = 3.03, m/z: 614.7 $[M+H]^+$.

EXAMPLE 99



6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (202 mg, 0.50 mmol), in *N,N*-dimethylformamide (4 ml) was added 5-methoxy-2-methyl-3-indole acetic acid (170 mg, 0.74 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide, hydrochloride (150 mg, 0.75 mmol), and 1-hydroxybenzotriazole (105 mg, 0.74 mmol). The mixture was stirred at room temperature for 12 hours. The crude reaction mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo, which afforded 2-amino-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

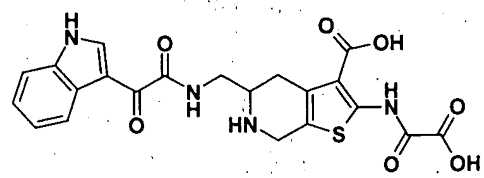
^{1}H-NMR ($CDCl_3$) δ 7.16 (d, 2H, *J* = 10.8 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 6.94 (m, 1H), 6.85 (dd, 1H, *J* = 8.4 Hz and *J* = 1.2 Hz), 6.78 (dd, 1H, *J* = 8.3 Hz

and J = 1.2 Hz), 6.65 (m, 3H), 6.57 (m, 4H), 3.57 (t, 4H, J = 3.0 Hz), 3.53 (m, 6H), 3.59-3.29 (m, 5H), 3.12-2.92 (m, 4H), 2.39 (s, 3H), 1.6 (s, 9H);
LC-MS R_t= 2.19, m/z: 605 $[M+H]^+$.

To a solution of 2-amino-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (96 mg, 0.5 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (583 mg, 3.0 mmol) and the reaction stirred at room temperature for 24 hours. The mixture was then concentrated in vacuo. The residue was purified by flash column chromatography (25% ethylacetate/dichloromethane) to give 53 mg (15 %) of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H-NMR ($CDCl_3$) δ 7.16 (d, 2H, J = 10.8 Hz), 6.99 (d, 1H, J = 2.5 Hz), 6.94 (m, 1H), 6.85 (dd, 1H, J = 8.4 Hz and J = 1.2 Hz), 6.78 (dd, 1H, J = 8.3 Hz and J = 1.2 Hz), 6.65 (m, 3H), 6.56 (m, 3H), 3.57 (m, 3H), 3.53 (m, 6H), 3.59-3.29 (m, 5H), 3.12-2.92 (m, 4H), 2.39 (s, 3H), 1.6 (s, 18H);
LC-MS R_t = 2.36 min, m/z: 733 $[M+H]^+$.

2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was dissolved in 50% trifluoroacetic acid/dichloromethane (3 ml) and stirred at room temperature for 48 hours. The solvent was removed in vacuo and the residual trifluoroacetic acid was removed under reduced pressure to give 17 mg (49 %) of the title compound as a solid trifluoroacetate.
^{1}H-NMR (DMSO-d_6) δ 10.62 (s, 1H), 7.31 (s, 1H), 7.08 (d, 1H, J = 10.2 Hz), 6.93 (s, 2H), 6.58 (dd, 1H, J_1 = 5.25 Hz and J_2 = 2.8 Hz), 3.84-3.44 (m, 19H, partially obscured by solvent), 2.95 (s, 1H), 2.28 (s, 3H), 1.31 (s, 1H), 1.19 (s, 2H);
LC-MS R_t = 1.89 min, m/z: 621 $[M+H]^+$.

EXAMPLE 100



5-((2-(1*H*-Indol-3-yl)-2-oxo-acetylamino)methyl)-2-(Oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (209 mg, 0.51 mmol) in dry *N,N*-dimethylformamide (4 ml) was added 3-indole-glyoxylic acid (141 mg, 0.74 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (152 mg, 0.76 mmol), and 1-hydroxy-benzotriazole (100 mg, 0.74 mmol). The mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (100 ml) and washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (2:5) as eluent, which afforded 143 mg (40 %) of 2-amino-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS R_t = 2.31 min, m/z: 574.9 $[M+H]^+$.

To a solution of 2-amino-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (143 mg, 0.25 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (144 mg, 0.75 mmol) and the flask was purged with nitrogen. After 24 hours an additional portion of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (169 mg, 0.86 mmol) was added and the reaction mixture allowed stirred for an additional 24 hours. The mixture was then concentrated in vacuo. The residue was purified by flash chromatography using a mixture of ethyl acetate/hexanes (2:5) as eluent, which afforded 101 mg (58 %) of 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-

methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a oil.

^{1}H-NMR ($CDCl_3$) δ 9.23 (s, 1H), 9.07 (d, 1H, *J* = 3.6 Hz), 8.50 (d, 1H, *J* = 7.6 Hz), 8.15 (d, 1H, *J* = 4.0 Hz), 7.47 (d, 2H, *J* = 7.2 Hz), 7.38-7.27 (m, 6H), 6.89 (d, 2H, *J* = 8.8 Hz), 3.87-3.59 (m, 6H), 3.04 (dd, 2H, *J* = 23.6 Hz), 2.74 (dd, 2H, J = 22.4 Hz), 1.62 (s, 18H);

LC-MS R_t = 2.49 min, m/z: 703 [M+H]$^+$.

2-(*tert*-Butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (101 mg, 0.143 mmol) was dissolved in dry tetrahydrofuran (6 ml) and passed through a pipette, plugged with cotton containing Raney 2800 Nickel (0.38 g). The pipette was flushed with dry tetrahydrofuran (6 ml) and the filtrate was concentrated in vacuo. Pd on carbon (10%, 102 mg, source: Avocado) and formic acid (10% in methanol, 5 ml) were added to the flask containing 2-(*tert*-Butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester. After stirring for 18 hours, the solution was filtered through a pad of celite and concentrated in vacuo. The residue was diluted in ethyl acetate, washed with saturated sodium bicarbonate (2 x 25 ml), brine (2 x 25 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was subjected to flash chromatography using a mixtureof 10% methanol/dichloromethane as eluent, which afforded 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR ($CDCl_3$) δ 9.23 (s, 1H), 9.07 (d, 1H, *J* = 3.6 Hz), 8.50 (d, 1H, *J* = 7.6 Hz), 8.15 (d, 1H, *J* = 4.0 Hz), 7.27 (s, 2H), 7.09 (d, 1H, *J* = 8.8 Hz), 6.81 (d, 1H, *J* = 8.8 Hz), 3.79 (s, 1H), 2.29 (s, 1H), 1.62-1.57 (m, 18H), 0.08 (s, 5H);

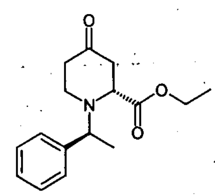
LC-MS: R_t = 2.17 min, m/z: 583 [M+H]$^+$.

The above 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was dissolved in 50% trifluoroacetic acid/dichloromethane (3 ml) and stirred at room temperature for 18 hours. The solvent was removed in vacuo and residual trifluoroacetic acid was removed under reduced pressure affording 17.1 mg of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6) δ 12.28 (s, 2H), 9.26 (s, 1H), 9.13 (s, 1H), 8.83 (d, 1H, J = 2.8 Hz), 8.26 (d, 1H, J = 8.8 Hz), 7.55 (d, 1H, J = 4.8 Hz), 7.27 (d, 2H, J = 7.6 Hz), 4.42 (d, 1H, J = 15.2 Hz), 4.29 (d, 1H, J = 16.4 Hz), 3.76-3.22 (m, 4H, partially obscured by solvent), 2.91-2.834 (m, 1H), 1.23 (s, 1H); LC-MS: R_t = 0.99 min, m/z 471.4 [M+H]$^+$.

GENERAL CHIRAL SYNTHESIS

4-Oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester

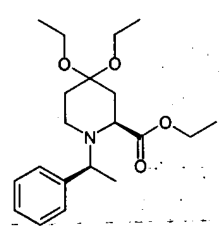


Dichloromethane (1L) and mol sieves 3 Å (113 g) and amine (S)-(-)α-methyl-benzylamin (71,7 ml) were mixed in a 2 l three-necked bottle cooled to –5 °C (using a ethanol/water/ice bath). A 50 % solution of ethylglyoxylate in toluene (117,6 ml) was added drop wise over 20 min., keeping the temperature between –5 °C and 0 °C The mixture was stirred for 0.5 hour before it was cooled to –30 °C. Trifluoroacetic acid (45,2 ml) was added over 3-4 minutes. Boron trifluoride diethyl ether (69,8 ml) was added drop wise over 5 min at –55 °C. The ice bath was removed and the mixture was allowed to warm up to –45 °C whereupon 2-(trimethylsilyloxy)-1,3-butadiene (100 ml) was added drop wise over 10 minutes. During the addition the mixture was cooled and the temperature

kept below –20 °C. The above additions are all exothermic hence the cooling bath should have sufficient capacity to remove the heat generated during the rapid addition. The reaction mixture was stirred for 2 hours at –15 °C and 1 hour at 0 °C and then poured on ice/water and stirred for 15 minutes. Solid sodium hydrogen carbonate was added until pH 7-8. The mixture was stirred overnight at room temperature. The layers wee separated and the aqueous phase extracted with dichloromethane. The combined organic phases were filtered through a plug of silica eluting with dichloromethane. The relevant fractions were concentrated in vacuo. The residue was dissolved in hot heptane and cooled. This leaves a yellowish gummy material on the side of the flask and crystals starts forming. The heptane solution was heated again to dissolve crystals, leaving the gummy material on the side of the flask and the mixture was filtered hot. The heptane solution was cooled to room temperature and the precipitate was filtered off and dried in vacuo, which afforded 38 g of 4-oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester as a solid.

The filtrate was put in a refrigerator and a second crop was formed which was less pure and needed recrystallization from heptane to yield another 7,5 g of 4-oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester.

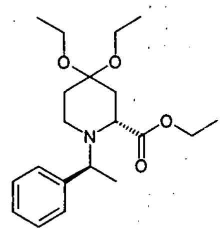
4,4-Diethoxy-1-((*S*)-1-phenyl-ethyl)-piperidine-(*S*)-2-carboxylic acid ethyl ester



The mother liquor from the above crystallization was concentrated in vacuo. 5.0 g of the resulting material (18.16 mmol) was dissolved in

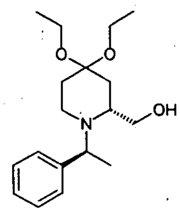
ethanol (100 ml) and triethylorthoformate (26.9 g, 181.6 mmol) and para-toluensulphonic acid (6.9 g, 36.32 mmol) was added. The reaction was stirred at room temperature for 16 hours before the mixture was poured on aqueous sodium hydrogen carbonate (200 ml) and extracted with ethyl acetate (4 x 75 ml). The combined extracts were concentrated in vacuo and purified by column chromatography (SiO_2, Flash 40, petrol ether-ethyl acetate 10:1). Collection of the first band (R_f = 0.68) gave 1.14 g (18 %) of 4,4-diethoxy-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester and collection of the second band (R_f = 0.4) gave 3.60 g (57 %) of the title compound.

4,4-Diethoxy-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester



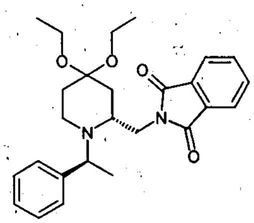
4-Oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester (11.0 g, 0.040 mmol) was dissolved in a 1:1 mixture of triethyl orthoformate and ethanol (140 ml) and *para*-toluene-4-sulphonic acid (15.2 g, 80 mmol) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was neutralized with sodium bicarbonate (to pH 7-8), and extracted with dichloromethane (3 x 100 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petrol ether/ethyl acetate 10:1), which afforded 12.0 g (86 %) of the title compound as an oil.

4,4-Diethoxy-1-((*S*)1-phenyl-ethyl)-(*R*)-2-hydroxymethyl-piperidine



To a solution of 4,4-diethoxy-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester (36.0 g, 0.103 mol) in dry diethyl ether (150 ml) was added a suspension of lithium aluminum hydride (5.88 g, 0.155 mol) in dry diethyl ether (300 ml) under an atmosphere of nitrogen at such a rate that the solution gently reflux. The reaction mixture was stirred over night before it was cooled to 0 °C and ethyl acetate (30 ml) was added drop wise to destroy excess lithium aluminum hydride. After stirring for another 0.5 hour, water (12 ml) was added drop wise. After stirring for 10-15 min the precipitate was filtered off through celite and the filter cage was washed with plenty of diethyl ether. The filtrate was washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent evaporated <u>in</u> <u>vacuo</u>, which afforded 30 g (95 %) of the <u>title</u> <u>compound</u> as an oil.

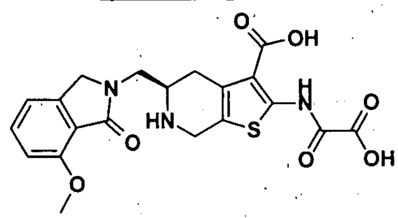
4,4-Diethoxy-1-((*S*)-1-phenyl-ethyl)-(*R*)-2-phthalimidomethyl-piperidine



A solution of 4,4-Diethoxy-1-((*S*)1-phenyl-ethyl)-(*R*)-2-hydroxymethyl-piperidine (65.35 g, 0.213 mmol), triphenylphosphine (61.3 g, 0.234 mol) and phthalimide (34.4 g, 0.234 mol) in tetrahydrofuran (700 ml) cooled to 0 °C was added diethyl azodicarboxylate over the course of 1.5 hour. The reaction mixture was stirred at 0 °C for another 2 hours before the solvent was removed <u>in</u> <u>vacuo</u>. The residue was dissolved in hot heptane-toluene (3:2) (650 ml) before it was cooled on an ice bath. The precipitate consisting of triphenyl phosphine oxide was filtered off and washed with heptane. The filtrate was concentrated <u>in</u> <u>vacuo</u> and the residue subjected

to column chromatography using a mixture of toluene-ethyl acetate-heptane (3:1:3) as eluent. The solvent was evaporated in vacuo whereupon a viscous oil was obtained. Upon addition of light petrol ether the product crystallized to give 67.4 g (73 %) of the title compound as a solid.

EXAMPLE 101



5-(*R*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A mixture of 4,4-diethoxy-1-((*S*)-1-phenyl-ethyl)-(*R*)-2-phthalimidomethyl-piperidine (5.25 g, 12.0 mmol) and hydrazine hydrate (2.92 ml, 60 mmol) was stirred overnight in ethanol (100 ml) at room temperature. The solvent was removed in vacuo and the solid residue was extracted with refluxing diethyl ether. The diethyl ether fractions were combined and evaporated in vacuo, which afforded 3.94 g (94 %) of 4,4-diethoxy-1-((*S*)-1-phenyl-ethyl)-(*R*)-2-aminomethyl-piperidine as an oil.

4,4-Diethoxy-1-((*S*)-1-phenyl-ethyl)-(*R*)-2-aminomethyl-piperidine (2.25 g, 7.37 mmol), and triethyl amine (1.49 g, 14.7 mmol) in acetonitrile (50 ml) was heated to 60 °C before 2-chlormethyl-6-methoxy-benzoic acid methyl ester (1.58 g, 7.37 mmol) in acetonitrile (25 ml) was added over the course of 1.5 hour. After addition the reaction mixture was stirred overnight at 60 °C. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (50 ml) and washed with saturated sodium bicarbonate. After drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo the residue was subjected to flash column chromatography (SiO_2, ethyl acetate-light petrol ether (1:1)) to give 2.3 g

(69 %) of 2-(*R*)-(7-methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4,4-diethoxy-1-(1-(*S*)-phenyl-ethyl)-piperidine.

2-(*R*)-(7-Methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4,4-diethoxy-1(1-(*S*)-phenyl-ethyl)-piperidine (2.0 g, 4.4 mmol) was dissolved in a ice cold mixture of trifluoroacetic acid and water (10 ml, 9:1) and stirred or 0.5 hour on an ice bath. The reaction mixture was poured on aqueous sodium carbonate (100 ml) and extracted with dichloromethane (2 x 50 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo, affording 1.67 g (100 %) of 2-(*R*)-(7-methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4-oxo-1(1-(*S*)-phenyl-ethyl)-piperidine.

2-(*R*)-(7-Methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4-oxo-1(1-(*S*)-phenyl-ethyl)-piperidine (1.67 g, 4.41 mmol), sulphur (0.155 g, 4.85 mmol), *tert*-butylcyanoacetate (0.684 g, 4.85 mmol), *N*-methylmorpholine (0.892 g, 8.82 mmol) and molecular sieves (4Å, 2 g) was heated to 50 °C in ethanol under an atmosphere of nitrogen for 16 hours. The reaction mixture was filtered through a plug (1 cm) of SiO_2, the silica was washed with dichloromethane-ethyl acetate and the solvent was removed in vacuo. The resulting residue was subjected to column chromatography (Flash 40, SiO_2, toluene-ethyl acetate (3:1)), which yielded 1.17 g (50 %) of 2-amino-5-(*R*)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester and 2-amino-7-(*S*)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester as a 3:1 mixture.

The above mixture of 5- and 7-regioisomers (1.17 g, 2.19 mmol) and imidazol-2-yl-oxo-acetic acid *tert*-butyl ester (1.29 g, 7.57 mmol) and triethylamine (0.66 g, 6.57 mmol) was stirred under an atmosphere of nitrogen in dichloromethane (25 ml) for 16 hours. The solvent was removed in vacuo and the residue was subjected to column chromatography (SiO_2, Flash 40, ethyl acetate-petrol ether (1:1)).

Collection of relevant fractions gave 0.61 g (42 %) of 2-(*tert*-butoxyoxalyl-amin)-5-(*R*)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

2-(*tert*-Butoxyoxalyl-amin)-5-(*R*)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.60 g, 0.91 mmol) was stirred for 16 hours in a mixture of methanol and formic acid (10:1) (20 ml) in the presence of 10 % palladium on carbon (50 % water). The reaction mixture was filtered through a plug of Celite and washed with methanol. The volatiles were removed <u>in vacuo</u> and the residue was dissolved in dichloromethane (50 ml), washed with semi saturated aqueous sodium carbonate (50 ml), dried ($MgSO_4$), filtered and the solvent evaporated <u>in vacuo</u>. The residue was purified by column chromatography (SiO_2, Flash 40, ethyl acetate-methanol (100:15)), which afforded 0.36 g (71 %) of 2-(*tert*-butoxyoxalyl-amin)-5-(*R*)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

2-(*tert*-Butoxyoxalyl-amin)-5-(*R*)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (349 mg, 0.63 mmol) was stirred for 16 hours in a mixture of trifluoroacetic acid and dichloromethane (1:1) (10 ml) whereupon diethyl ether (20 ml) was added. The precipitate was filtered off and washed with diethyl ether, which afforded 215 mg (61 %) of the <u>title compound</u> as a solid trifluoroacetate.

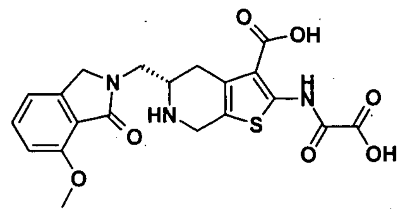
LC-MS: R_t = 1.17 min, m/z: 446 $[M+H]^+$

Calculated for $C_{20}H_{19}N_3O_7S$, $C_2HF_3O_2$, 0.5xH_2O

C, 46.48%; H, 3.72%; N, 7.39%; Found:

C, 46.45%; H, 3.97%; N, 7.43%;

EXAMPLE 102



5-(*S*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 4,4-diethoxy-1-((*S*)-1-phenyl-ethyl)-piperidine-(*S*)-2-carboxylic acid ethyl ester (35.98 g, 0.103 mol) in diethyl ether (150 ml) was added drop wise to a suspension of lithium aluminum hydride (5.88 g, 0.155 mol) in diethyl ether (300 ml) over the course of 1 hour. The reaction mixture was stirred at room temperature overnight before it was cooled on an ice bath and the reaction was quenched by dropwise addition of ethyl acetate (30 ml), followed by drop wise addition of water (12 ml) whereupon a gray precipitate was formed. The mixture was filtered through a plug of Celite and the filter cage was washed with plenty of diethyl ether. The filtrate was dried ($MgSO_4$) before it was filtered and the solvent removed in vacuo, which afforded 24.5 g (79 %) of 4,4-diethoxy-1-(1-(*S*)-phenyl-ethyl)-(*S*)-2-hydroxymethyl-piperidine as an oil.

A suspension of 4,4-diethoxy-1-(1-(*S*)-phenyl-ethyl)-(*S*)-2-hydroxymethyl-piperidine (20 g, 65 mmol), triphenylphosphine (18.76 g, 72 mmol) and phthalimide (10.52 g, 72 mmol) in tetrahydrofurane (200 ml) cooled to 0 °C was added diethyl azodicarboxylate (11.34 ml, 72 mmol) over the course of 1 hour. The reaction mixture was stirred at 0 °C for another 2 hours before the volatiles were removed in vacuo. The residue was dissolve in hot heptane-toluene (3:2) (100 ml) before it was cooled on an ice bath. The precipitate was filtered off and washed with heptane. The filtrate was concentrated in vacuo and the residue subjected to column chromatography using a mixture of toluene/ethyl acetate/heptane (3:1:3) as eluent. The solvent was evaporated in vacuo and the residue was crystallized by addition of light petrol ether (250 ml). The precipitate was

filtered off, which afforded 24 g (85 %) of 4,4-diethoxy-1-(1-(*S*)-phenyl-ethyl)-2-(*S*)-phthalimidomethyl-piperidine as a solid.

4,4-Diethoxy-1-(1-(*S*)-phenyl-ethyl)-2-(*S*)-phthalimidomethyl-piperidine (4.0 g, 9.2 mmol) was dissolved in a mixture of trifluoroacetic acid and water (9:1) (100 ml) at 0 °C and stirred for 2 hours at this temperature. The mixture was basified with half saturated aqueous sodium carbonate, extracted with ethyl acetate and dried ($MgSO_4$) for 2 hours. The solvent was removed in vacuo and the residue was dried in a vacuum own at 40 °C for to days. This afforded 3.23 g (98 %) of 4-oxo-1-(1-(*S*)-phenyl-ethyl)-2-(*S*)-phthalimidomethyl-piperidine pure without further purification (98 %). A mixture of 4-oxo-1-(1-(*S*)-phenyl-ethyl)-2-(*S*)-phthalimidomethyl-piperidine (17.28 g, 47.73 mmol), *tert*-butylcyanoacetat (7.41 g, 52.17 mmol), sulphur (1.71 g, 52.17 mmol) and morpholine (8.31 g, 95.46 mmol) in ethanol (150 ml) was heated under an atmosphere of nitrogen at 50 °C. The volatiles were removed in vacuo and the residue was subjected to column chromatography on silica gel (heptane-ethyl acetate 5:1). The fractions consisting of a mixture of 5- and 7-isomer were collected and the solvent evaporated in vacuo. The residue was purified on a reverse phase (C_{18}) column using a Flash 40 system. The residue was applied in a minimum volume of acetonitrile and eluted with 40 % acetonitrile in water containing 0.1 % trifluoroacetic acid. When the 5-isomer was collected the eluent was changed to 50 % acetonitrile in water with 0.1 % trifluoroacetic acid and the 7-isomer was collected. Yield of 2-amino-5-(*S*)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester was 7.96 g and yield of 2-amino-7-(*R*)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester was 3.72 g (47 % total).

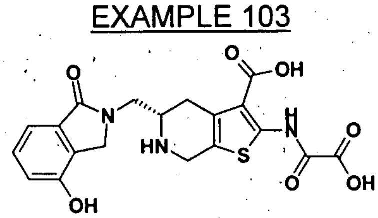
2-Amino-5-(*S*)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (7.96 g, 15.4 mmol) and hydrazine hydrate (3.85 g, 77.0 mmol) in

ethanol (250 ml) was stirred for 16 hours at room temperature. The solvent was removed in vacuo and the solid residue was extracted with diethyl ether (3 x 200 ml). The fractions were combined and the solvent removed in vacuo to give 5.9 g (100 %) of 2-amino-5-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester.

2-Amino-5-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (0.55 g, 1.42 mmol) and triethylamine (396 μl, 2.84 mmol) was heated in acetonitrile (15 ml) under an atmosphere of nitrogen to 60 °C whereupon a solution of 2-chloromethyl-6-methoxy-benzoic acid methyl ester (0.32 g, 1.49 mmol) in acetonitrile (5 ml) was added dropwise over the course of 3 hours, keeping the reaction mixture at 60 °C. The reaction was allowed to cool to room temperature and was left for 16 hours before the solvent was evaporated in vacuo. The product was purified by column chromatography (SiO_2, Flash 40, ethyl acetate-petrol ether) to give 400 mg (53 %) of 2-amino-5-(*S*)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-((*S*)-1-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

The title compound was obtained as a trifluoroacetate in a similar way as described in example 101 using the last three steps.

EXAMPLE 103



5-(*S*)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

3-Hydroxy-2-methylbenzoic acid (0.5 g, 3.2 mmol) was dissolved in HPLC grade methanol (5 ml) and cooled to 0 °C under nitrogen. Acetyl chloride (5 ml) was added dropwise. Once the addition was complete, the ice bath was removed and the reaction mixture allowed warming to room temperature over a period of 18 hours. The reaction was complete by tlc (R_f=0.5, 1:1 ethyl acetate/hexanes) and quenched with saturated sodium bicarbonate. The reaction mixture was concentrated, diluted with dichloromethane and water and the layers separated. The aqueous layer was extracted with dichloromethane (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo, which afforded 0.5 g (91 %) of 3-hydroxy-2-methylbenzoic acid methyl ester as a solid.

^{1}H-NMR ($CDCl_3$) δ 7.39 (dd, 1H, J = 8.1 Hz and J = 1.5 Hz), 7.09 (t, 1H, J = 8.1 Hz), 6.92 (dd, 1H, J = 8.1 Hz and J = 1.2 Hz), 5.11 (bs, 1H), 3.87 (s, 3H), 2.43 (s, 3H).

3-Hydroxy-2-methylbenzoic acid methyl ester (0.5 g, 3.01 mmol) in dichloromethane (15 ml) and *N,N*-diisopropylethylamine (1.57 ml, 9.03 mmol) was cooled to 0 °C under nitrogen. Chloromethyl methyl ether (0.46 ml, 6.02 mmol) was added dropwise and the reaction allowed warming to room temperature over a period of 18 hours. The reaction was judged to be 50 % complete by tlc (1:2 ethyl acetate/hexanes, I_2) and therefore, *N,N*-diisopropylethylamine (1.57 ml, 9.03 mmol) was added, the reaction mixture cooled to 0 °C and chloromethyl methyl ether (0.46 ml, 6.02 mmol) added once more. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction was quenched with water and the layers separated. The aqueous layer was extracted once with dichloromethane and the organic layers combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (20 % ethyl acetate/hexanes) affording 0.44 g (69 %) of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 7.46 (dd, 1H, J = 7.6 Hz and J = 1.2 Hz), 7.21 (dd, 1H, J = 8 Hz and J = 1.2 Hz), 7.18 (d, 1H, J = 8 Hz), 5.21 (s, 2H), 3.88 (s, 3H), 3.48 (s, 3H), 2.46 (s, 3H).

To a mixture of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester (0.44 g, 2.09 mmol) in carbon tetrachloride (10 ml) was added *N*-bromosuccinimide (0.39 g, 2.19 mmol) and 1,1'-azo bis(cyclohexane-carbonitrile) (0.051 g, 0.21 mmol). The mixture was heated at reflux for 3 hours, at which time the reaction was judged complete by tlc (1:4 ethyl acetate/hexanes). The reaction mixture was cooled to room temperature and concentrated in vacuo to a solid. The solid was recrystallized from hexane leaving 0.44 g (82 %) of 2-bromomethyl-3-methoxymethoxy-benzoic acid methyl ester as a solid.

^{1}H-NMR ($CDCl_3$) δ 7.58 (dd, 1H, J = 6.8 Hz and J = 2.4 Hz), 7.33-7.29 (m, 2H), 5.30 (s, 2H), 5.07 (s, 2H), 3.94 (s, 3H), 3.52 (s, 3H).

To a stirred mixture of 2-amino-5-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (0.24 g, 0.67 mmol) in acetonitrile (30 ml) was added *N,N*-diisopropylethylamine (0.16 ml, 0.93 mmol) under nitrogen. 2-Bromo-methyl-3-methoxymethoxy-benzoic acid methyl ester (0.16 g, 0.55 mmol) dissolved in acetonitrile, was added via syringe pump at a rate of 0.3 ml/hour. Once the addition was complete, the reaction mixture was stirred at room temperature for 24 hours. Tlc analysis (1:1 ethyl acetate/hexanes) indicated the reaction to be complete. The volatiles were removed in vacuo and the resultant oil dissolved in ethyl acetate/water. The layers were separated and the aqueous layer extracted with ethyl acetate (3x). The organic layers were combined, dried ($MgSO_4$), filtered and the solvebt evaporated in vacuo, which afforded 0.34 g (100 %) of 2-amino-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester, which was used without further purification in the next step.

^{1}H-NMR ($CDCl_3$) δ 7.51 (d, 1H, J = 6.8 Hz), 7.42 (t, 2H, J = 7.6 Hz), 7.23-7.17 (m, 5H), 5.93 (s, 2H), 5.25 (s, 2H), 4.23 (s, 2H), 4.12 (q, 1H, J = 7.2

Hz), 3.94 (m, 1H), 3.85 (q, 1H, J = 6.4 Hz), 3.66 (d, 1H, J = 16.4 Hz), 3.50 (s, 3H), 3.48-3.46 (m, 1H), 3.20 (dd, 1H, J = 14 Hz and J = 6 Hz), 2.94-2.87 (m, 1H), 2.60 (m, 1H), 1.49 (s, 9H), 1.36 (d, 3H, J = 6.4 Hz);
LC-MS: m/z: 564.1 $[M+H]^+$.

To a solution of 2-amino-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.34 g, 0.60 mmol) in dichloromethane (10 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.35 g, 1.8 mmol). The reaction mixture was stirred at room temperature for 18 hours and the solvent concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water (2 x 20 ml) and brine (2 x 25 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (1:1) as eluent. The obtained residue was then subjected to chromatotron purification (1% methanol/ dichloromethane) and later to another flash chromatography (20 % ethyl acetate/hexanes to 25 % ethyl acetate/hexanes) to obtain 210 mg (50 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H-NMR ($CDCl_3$) δ 12.50 (s, 1H), 7.51 (dd, 1H, J = 6.8 Hz and J = 1.2 Hz), 7.42 (t, 2H, J = 8 Hz), 7.25-7.17 (m, 5H), 5.23 (s, 2H), 4.24 (q, 2H, J = 16.8 Hz), 4.08 (d, 1H, J = 16.8 Hz), 4.01 (dd, 1H, J = 14 Hz and J = 8.8 Hz), 3.89 (d, 1H, J = 17.6 Hz), 3.82 (q, 1H, J = 6.8 Hz), 3.56 (q, 1H, J = 6.4 Hz), 3.51 (s, 3H), 2.28 (dd, 1H, J = 14 Hz and J = 6.4), 2.98-2.92 (m, 1H), 2.69 (d, 1H, J = 17.2), 1.56 (s, 9H), 1.54 (s, 9H), 1.38 (d, 3H, J = 6.8 Hz);
LC-MS: m/z: 692.5 $[M+H]^+$.

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.16 g,

0.23 mmol) in formic acid (10 % in methanol, 5 ml total) was added 10% palladium on carbon (85 mg, source: Avacado) and the reaction mixture allowed to stir at room temperature. After 6 hours, tlc (1:1 ethyl acetate/hexanes) analysis indicated reaction complete. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The crude product was purified via flash chromatography (gradient: 3% isopropyl alcohol/dichloromethane to 5 % isopropyl alcohol/dichloromethane (in 1% increments of isopropyl alcohol)) to provide 0.11 g (82 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 12.50 (bs, 1H), 7.48 (dd, 1H, J = 7.6 Hz and J = 0.8 Hz), 7.38 (t, 1H, J = 8 Hz), 7.22 (dd, 1H, J = 8 Hz and J = 0.8 Hz), 5.24 (s, 2H), 4.50 (q, 2H, J = 17.3 Hz), 4.02-3.90 (m, 2H), 3.74 (ddd, 2H, J = 34 Hz, J = 13.6 Hz and J = 5.6 Hz), 3.49 (s, 3H), 3.24 (m, 1H), 2.97 (ddd, 1H, J = 20 Hz, J = 4.4 Hz and J = 2.8 Hz), 2.50 (m, 1H), 1.59 (s, 9H), 1.51 (s, 9H);

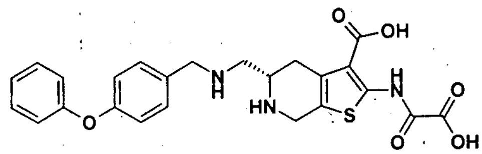
LC-MS: m/z: 587.8 $[M+H]^+$.

2-(*tert*-Butoxyoxalyl-amino)-5-(*S*)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.11 g, 0.18 mmol) was dissolved in neat trifluoroacetic acid (4 ml) and stirred at room temperature for 48 hours. The reaction mixture was concentrated in vacuo and the resultant solid washed with dichloromethane several times affording 100 mg (83 %) of the title compound as a solid trifluoroaceatet.

^{1}H-NMR (DMSO-d_6) δ 12.29 (bs, 1H), 10.13 (s, 1H), 9.29 (bs, 1H), 9.10 (bs, 1H), 7.32 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.01 (d, 1H, J = 8 Hz), 4.52 (d, 1H, J = 17.2 Hz), 4.40-4.22 (m, 3H), 4.05 (dd, 1H, J = 14.4 Hz and J = 9.6 Hz), 3.90 (bs, 1H), 3.69 (dm, 1H), 3.22 (dm, 1H), 2.80 (dm, 1H);

LC-MS: m/z: 432.2 $[M+H]^+$.

EXAMPLE 104



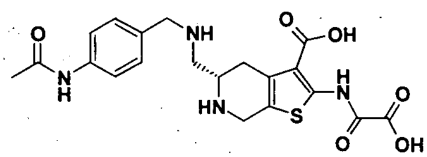
2-(*S*)-(Oxalyl-amino)-5-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 2-amino-5-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (500 mg, 1.29 mmol) and 4-phenoxybenzaldehyde (256 mg, 1.29 mmol) was heated to 50 °C in ethanol (50 ml) for 1 hour in the presence of molecular sieves (4 A, 5 ml). The reaction mixture was cooled on an ice bath before sodium borohydride (98 mg, 2.59 mmol) was added in three portions over 45 min. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. The mixture was filtered through a plug of Celite and the filter cage was washed with dichloromethane (3 x 25 ml). The solvent was removed in vacuo and the residue was redissolved in ethyl acetate (50 ml), washed with sodium bicarbonate (50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo before the residue was redissolved in acetonitrile (20 ml). Triethylamine (130 mg, 1.29 mmol), di-*tert*-butyl dicarbonate (282 mg, 1.29 mmol) and 4-(*N,N*-dimethyl-amino)pyridine (5 mg, cat.) was added and the reaction mixture was stirred for 16 hours at room temperature. The volatiles were removed in vacuo and ethyl acetate (50 ml) was added and the solution was washed with saturated sodium bicarbonate (50 ml) and dried ($MgSO_4$). The crude product was purified by column chromatography (SiO_2, petroleum ether-ethyl acetate (9:1)) to give 325 mg (38% overall) of 2-amino-5-(*S*)-((4-phenoxy-benzylamino)methyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester.

The title compound was obtained as a trifluoroacetate in a similar way as described in example 96 using the last three steps.
Oxalation: Standard procedure (16 hours, 82 %)
Hydrogenolysis: standard procedure (Pd/C, 10% Pd, methanol-formic acid, 16 hours, ((10:1)) (82% yield)
TFA cleavage: Standard procedure. Yield 150 mg (87%).

LC-MS m/z: 482 $[M+H]^+$, R_t = 1.87 min
Calculated for $C_{24}H_{23}N_3O_6S$, $2x(C_2HF_3O_2)$
C, 47.40%; H, 3.55%; N, 5.92%; Found:
C, 47.47%; H, 3.87%; N, 5.88%;

EXAMPLE 105

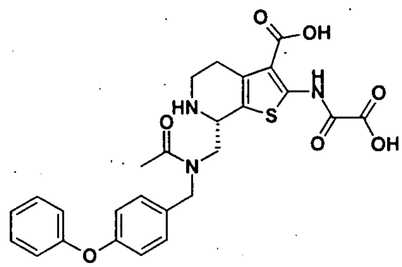


5-(*S*)-((4-Acetylamino-benzylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared as a trifluoroacetate in a similar way as described in Example 96 using 2-amino-5-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester and *N*-(4-formyl-phenyl)acetamide as the starting material.

Calculated for $C_{20}H_{22}N_4O_6S$, $1.5xC_2HF_3O_2$, $1.5xH_2O$
C, 43.78%; H, 3.99%; N, 8.88%; Found:
C, 44.20%; H, 4.43%; N, 8.75%;

EXAMPLE 106



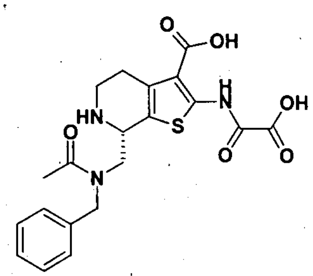
7-(*S*)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid

A solution of 2-amino-7-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic aicd *tert*-butyl ester (500 mg, 1.29 mmol) and 4-phenoxybenzaldehyde (256 mg, 1.29 mmol) was heated to 50 °C in ethanol (50 ml) for 1 hour in the presence of molecular sieves (4 A, 5 ml). The reaction mixture was cooled on an ice bath before sodium borohydride (98 mg, 2.59 mmol) was added in three portions over 45 min. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. The mixture was filtered through a plug of Celite and the filter cage was washed with dichloromethane (3 x 25 ml). The solvent was removed in vacuo and the residue was redissolved in ethyl acetate (50 ml), washed with sodium bicarbonate (50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo before the product was dissolved in dichloromethane (10 ml). The solution was cooled on an ice bath before di-isopropyl-ethyl amine (101 mg, 1.29 mmol) was added followed by drop wise addition of acetyl chloride (101 mg, 1.29 mmol) in dichloromethane (1 ml). The reaction mixture was stirred 1 hour at 0 °C and the solution was washed with sodium bicarbonate (10 ml) and dried ($MgSO_4$). The crude product was purified by flash column chromatography (SiO_2, ethyl acetate-petrol ether 1:3) to give 320 mg (41%) of 7-(*S*)-((acetyl-(4-phenoxy-benzyl)amino)methyl)-2-amino-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid

The title compound was obtained as a trifluoroacetate in a similar way as described in example 96 using the last three steps.
Oxalation: Standard procedure (Yield 69%)
Hydrogenolysis and trifluoroacetic acid cleavage in one step, Standard procedure (Overall yield 6%)

LC-MS m/z = 524 $[M+H]^+$, R_t = 2.58 min
Calculated for $C_{26}H_{25}N_3O_7S$, $C_2HF_3O_2$, $0.5xH_2O$
C, 52.01%; H, 4.21%; N, 6.50%; Found:
C, 51.82%; H, 4.34%; N, 6.36%.

EXAMPLE 107



7-(*S*)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid

A solution of 2-amino-7-(*S*)-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic aicd *tert*-butyl ester (400 mg, 1.03 mmol) and benzaldehyde (105 mg, 1.03 mmol) was heated to 50 °C in ethanol (20 ml) for 1 hour in the presence of molecular sieves (4 A, 7 ml). The reaction mixture was cooled on an ice bath before sodium borohydride (78 mg, 2.06 mmol) was added in three portions over 45 min. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. The mixture was filtered through a plug of Celite and the filter cage was washed with dichloromethane (3 x 25 ml). The solvent was removed in vacuo and the residue was redissolved in ethyl acetate (50 ml), washed with sodium bicarbonate (50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo before the product was dissolved in dichloromethane (20 ml). The solution was cooled on an ice

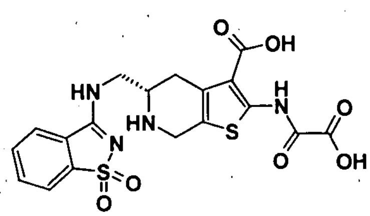
bath before di-isopropyl-ethyl amine (267 mg, 2.06 mmol) was added followed by drop wise addition of acetyl chloride (81 mg, 1.03 mmol) in dichloromethane (1 ml). The reaction mixture was stirred 1 hour at 0 °C before sodium bicarbonate (20 ml) was added. The mixture was extracted with dichloromethane (2 x 10 ml) and the combined organic fractions were dried ($MgSO_4$). The crude product was purified by flash column chromatography (petrol ether/ethyl acetate (3:1)), which afforded 250 mg (46 %) of 7-(*S*)-((acetyl-benzyl-amino)methyl)-2-amino-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

The title compound was obtained as a trifluoroacetate in a similar way as described in example 96 using the last three steps.

Oxalation: Standard procedure (54%)
Hydrogenolysis: Standard procedure (methanol-formic acid (10:1)) Yield 38 mg (26%)
Trifluoroacetic acid cleavage: Standard procedure 33 mg (80%)

LC-MS m/z: 432 $[M+H]^+$, R_t = 1.52 min
Calculated for $C_{20}H_{21}N_3O_6S$ x $1.5xC_2HF_3O_2$, $2xH_2O$
C, 43.26%; H, 4.18%; N, 6.58%; Found:
C, 43.19%; H, 3.86%; N, 6.46%.

EXAMPLE 108



5-(*S*)-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of (*S*)-2-amino-5-aminomethyl-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid *tert*-butyl ester (1.0 g, 2.58 mmol) in dichloromethane (10 ml) at 0 °C was added *N,N*-diisopropylethylamine (0.54 ml, 5.16 mmol). A solution of 3-chloro-benzo[d]isothiazole 1,1-dioxide (0.52 g, 2.58 mmol) in dichloromethane (10 ml) was then added dropwise and stirred for 30 min. The solution was warmed to room temperature and washed with water and dried ($MgSO_4$). The solvent was then removed in vacuo. The residue was taken into dichloromethane (15 ml) and imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (1.0 g, 5.16 mmol) was added. The solution was stirred for 2 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (100 ml). The solution was washed with 0.5 N hydrochloric acid solution, saturated sodium bicarbonate and brine, dried ($MgSO_4$) and filtered. The solvent was removed in vacuo. The residue was chromatographed using a mixture of 0-5% ethyl acetate/dichloromethane as eluent, which afforded 0.6 g (34 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-((1,1-dioxo-1*H*-benzo[d] isothiazol-3-ylamino)methyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil
^{1}H-NMR ($CDCl_3$) δ 12.50 (s, 1H), 7.94-7.92 (m, 1H), 7.79-7.71 (m, 2H), 7.59-7.50 (m, 1H), 7.38-7.27 (m, 4H), 6.86 (d, 1H, J=4 Hz), 4.14 (d, 1H, J=12 Hz), 3.95 (d, 1H, J=17 Hz), 3.88 (q, 1H, J=6 Hz), 3.70-3.62 (m, 1H), 3.47 (t, 1H, J=13 Hz), 3.34-3.24 (m, 1H), 3.06 (dd, 1H, J=17, 6 Hz), 2.53 (d, 1H, J=17 Hz), 1.62 (s, 9H), 1.61 (s, 9H), 1.44 (d, 3H, J=7 Hz).

A solution of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-((1,1-dioxo-1*H*-benzo[d] isothiazol-3-ylamino)methyl)-6-(1-(*S*)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (252 mg, 0.37 mmol) in tetrahydrofuran (12 ml) was passed through Raney Ni (0.95 g, 50% Raney Ni-Water washed with methanol (6 ml) and tetrahydrofuran (10 ml) and dried before use). The solvent was removed in vacuo. The residue was dissolved in acetic acid (7 ml) and hydrogenated with 10% Pd/C (250 mg) at 50 psi for 15 hours. The mixture was filtered and the filtrate was added to saturated sodium bicarbonate solution. The solution was then

extracted with ethylacetate (3 x 100 ml). The extracts were combined and dried ($MgSO_4$). The solvent was removed in vacuo. The residue was washed with diethyl ether affording 156 mg (73 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-((1,1-dioxo-1*H*-benzo[d] isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 12.59 (s, 1H), 7.94-7.90 (m, 1H), 7.70-7.66 (m, 3H), 7.51 (s, 1H), 4.11 (d, 1H, J=12 Hz), 4.08 (q, 2H, J=17 Hz), 3.40 (dd, 1H, J=12, 6 Hz), 3.26-3.18 (m, 1H), 3.18 (d, 1H, J=17 Hz), 2.55 (dd, 1H, J=12, 6 Hz), 1.62 (s, 18H).

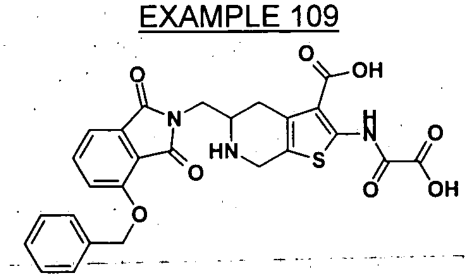
LC-MS: R_t = 3.58 min, m/z: 577 $[M+H]^+$.

A solution of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-((1,1-dioxo-1*H*-benzo[d] isothiazol-3-ylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (149 mg, 0.26 mmol) in 50 % trifluoroacetic acid/dichloromethane (1 ml) was left in an open flask for 60 hours. The volatiles were removed in vacuo and the residue was washed with dichloromethane to yield 80 mg (54 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6) δ 12.29 (s, 1H), 9.80 (s, 1H), 9.51 (bs, 2H), 8.19 (d, 1H, J=5 Hz), 8.02-8.00 (m, 1H), 7.89-7.84 (m, 2H), 4.46 (d, 1H, J=16 Hz), 4.30 (d, 1H, J=16 Hz), 3.96-3.80 (m, 3H), 3.30 (d, 1H, J=17 Hz), 2.93 (dd, 1H, J=18, 10 Hz);

LC-MS: R_t = 0.68 min, m/z: 465 $[M+H]^+$.

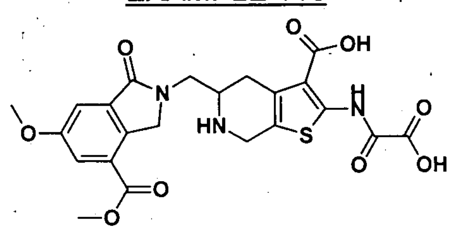
EXAMPLE 109



5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 52 as a trifluoroacetate.
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.25 (bs, 2H), 7.80 (t, 1H, J = 8 Hz), 7.59-7.32 (m, 7H), 5.37 (s, 2H), 4.42-4.21 (m, 2H), 3.95-3.70 (m, 3H), 3.4-3.2 (obscured by water, 1H), 2.83-2.75 (m, 1H)
LC-MS: R_t = 2.16 min, m/z: 536.1 $[M+H]^+$

EXAMPLE 110



5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (57.4 mg, 0.142 mmol) and diisopropyl ethylamine (49 μl, 0.28 mmol) in acetonitrile (20 ml) at room temperature was added 2-bromomethyl-5-methoxy-isophthalic acid dimethyl ester (3.00 g, 7.45 mmol). The solution was stirred for 16 hours and the solvent evaporated in vacuo. The residue was taken into ethyl acetate (50 ml) and washed with water (2 x 20 ml), 1 N hydrochloric acid (20 ml), brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:1) as eluent, which afforded 62 mg (71 %) of 2-amino-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-

tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR δ ($CDCl_3$): δ 7.75 (d, 1H, J = 2.4 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.11 (bs, 2H), 6.74 (d, 2H, J = 8.0 Hz), 5.97 (s, 2H), 4.71 (d, 1H, J = 18.4 Hz), 4.62 (d, 1H, J = 18.4 Hz), 4.09 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.80 (m, 1H), 3.76 (s, 3H), 3.66-3.40 (m, 5H), 2.80 (d, 1H, J = 17.2 Hz), 2.64 (d, 1H, J = 17.2 Hz), 1.52 (s, 9H).

To a stirred solution of 2-amino-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxy-carbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (60 mg, 0.10 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (60 mg, 0.30 mmol) in tetrahydrofuran (1.0 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (20 ml) and washed with 0.5 N hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml) and brine (10 ml), dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and residue was chromatographed using a gradient ethyl acetate/hexane (10-25 %) as eluent, which afforded 40 mg (58 %) of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR δ ($CDCl_3$): δ 12.54 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.10 (d, 2H, J = 8.0 Hz), 6.74 (d, 2H, J = 8.0 Hz), 4.74 (d, 1H, J = 18.4 Hz), 4.62 (d, 1H, J = 18.4 Hz), 4.05-3.90 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.82-3.48 (m, 5H), 3.77 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 2.67 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 1.61 (s, 9H), 1.58 (s, 9H).

To a solution of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester

(38 mg, 0.055 mmol) in 10 % formic acid/methanol (1.0 ml) at room temperature under nitrogen was added 10 % Pd/C (38 mg). The mixture was stirred for 16 hours and the Pd/C was filtered off and the filtrate evaporated in vacuo. The residue was taken into dichloromethane (1.0 ml) poured into hexane. The precipitate was filtered off, affording 28 mg (82 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

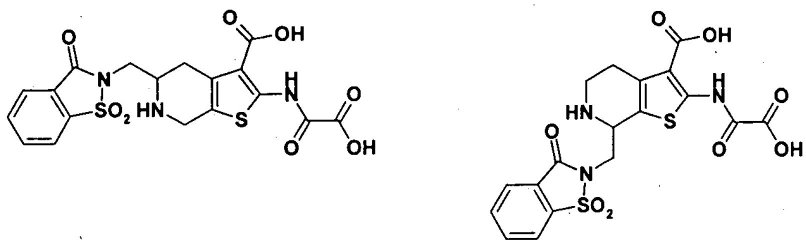
^{1}H-NMR δ ($CDCl_3$): δ 12.45 (s, 1H), 10.90 (s, 1H), 10.69 (s, H), 7.73 (s, 1H), 7.42 (s, 1H), 4.85 (bs, 2H), 4.65 (bs, 1H), 4.42 (bs, 2H), 3.99 (bs, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.35 (bs, 1Hz), 3.21 (bs, 1H), 1.62 (s, 9H), 1.56 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (14 mg, 0.023 mmol). The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into diethyl ether (20 ml). The precipitate was filtered off, which afforded 10 mg (75 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR δ (DMSO-d_6): δ 12.28 (s, 1H), 9.32 (s, 1H), 9.10 (s, 1H), 7.65 (d, 1H, J = 2.4 Hz), 7.50 (d, 1H, J = 2.4 Hz), 4.82 (d, 1H, J = 17.2 Hz), 4.65 (d, 1H, J = 17.6 Hz), 4.40 (d, 1H, J = 17.6 Hz), 4.30 (m, 1H), 4.10 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.95 (s, 1H), 3.89 (s, 6H), 3.85 (d, 1H, J = 17.2 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz).

LC-MS: R_t = 1.30 min; m/z: 504 $[M+H]^+$

EXAMPLE 111



2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid
and
2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-aminomethyl-4-(2-spiro[1,3]dioxolane)-piperidine (193 mg, 1.12 mmol) and diisopropyl ethylamine (0.46 ml, 2.55 mmol) in acetonitrile (10 ml) cooled to 0 °C was added 2-chlorosulfonyl-benzoic acid methyl ester (278 mg. 1.18 mmol). The solution was stirred at 25 °C for 24 hours. Solvent was removed in vacuo and the residue was chromatographed using a mixture of ethyl acetate/hexane (1:3) as eluent, which afforded 199 mg (51 %) of 2-(4-(2-spiro[1,3]dioxolane)piperidin-2-ylmethyl)-1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-one as a solid.
^{1}H-NMR ($CDCl_3$): δ 7.99-7.96 (m, 1H), 7.66-7.53 (m, 3H), 5.01 (s, 1H), 4.73 (dm, 1H, J = 14.4 Hz), 4.06-3.93 (m, 6H), 3.25 (dd, 1H, J = 12.6 Hz), 3.06 (td, 1H, J = 13.5 Hz and J = 3.6 Hz), 1.93 (dd, 1H, J = 14.1 Hz and J = 5.7 Hz), 1.87 (dd, 1H, J = 14.1 Hz and J = 3.0 Hz), 1.76 (dd, 1H, J = 13.5 Hz and J = 5.1 Hz).
LC-MS: R_t = 1.78; m/z: 339 $[M+H]^+$.

2-(4-(2-Spiro[1,3]dioxolane)piperidin-2-ylmethyl)-1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-one (199 mg, 0.588 mmol) was dissolved in 2 M hydrochloric acid (12 ml) and the solution was heated to 50 °C for 24 hours. The volatiles were removed in vacuo and the residue (341 mg) was treated without further purification with saturated sodium carbonate (12 ml), dichloromethane (8 ml) and di-t-butyl dicarbonate (1.64 g, 7.5 mmol). The mixture was stirred at 35 °C for 3 days and extracted with

dichloromethane (30 ml). The organic solution was washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:3) as eluent, which afforded 115 mg (50 %) of 4-oxo-2-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ 8.06 (dd, 1H, J = 6.0, 1.8 Hz), 7.95-7.80 (m, 3H), 5.02 (bs, 1H), 4.35 (bs, 1H), 3.91(dd, 1H, J = 15.0 Hz and J = 8.4 Hz), 3.78 (dd, 1H, J = 14.7 Hz and J = 5.7 Hz), 3.53 (t, 1H, J = 10.8 Hz), 2.74 (dd, 1H, J = 15.0 Hz and J = 7.5 Hz), 2.60-2.38 (m, 3H), 1.32 (s, 9H).

To a solution of 4-oxo-2-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (115 mg, 0.292 mmol) in absolute ethanol (5 ml) was added t-butyl cyanoacetate (57 μl, 0.41 mmol), sulfur (13 mg, 0.41 mmol) and morpholine (55 μl, 0.63 mmol). The solution was stirred at 50 °C for 14 hours. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:4) as eluent, which afforded 100 mg (62 %) of 2-amino-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a mixture.

^{1}H-NMR ($CDCl_3$): δ 8.10-8.00 (m, 1H), 7.98-7.77 (m, 2.8H), 7.66-7.58 (m, 0.2H), 6.11 (s, 0.4H), 6.06 (s, 0.6H), 5.59 (m, 0.2H), 5.39 (t, 0.3H, J = 5.7 Hz) 5.23 (bs, 0.3H), 5.04 (bs, 0.4H), 4.77 (d, 0.4H, J = 14.4 Hz), 4.60 (d, 0.4H, J = 14.4 Hz), 4.45-4.18 (m, 1H), 4.02-3.82 (m, 1.5H), 3.64 (dd, 0.5H, J = 14.7 Hz and J = 5.2 Hz), 3.30-2.60 (m, 2H), 1.54 (s, 7H), 1.53 (s, 2H), 1.26 (s, 7H), 1.21 (s, 2H).

To a stirred solution of the above 2-amino-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-

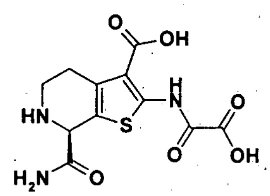
dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester mixture (100 mg, 0.18 mmol) in acetonitrile (7 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (290 mg, 1.46 mmol) in acetonitrile (1 ml). The mixture was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was taken into ethyl acetate. The solution was washed with 0.5 N hydrochloric acid solution, saturated sodium bicarbonate, brine, dried $MgSO_4$) and filtered. The solvent was removed in vacuo and the residue was chromatographed on silicagel using a mixture of ethyl acetate/hexane (1:4) as eluent, which provided 98 mg (80 %) of a mixture of 2-(*tert*-butoxyoxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-(*tert*-butoxyoxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.
^{1}H-NMR ($CDCl_3$): δ 12.60 (s, 0.3H), 12.54 (s, 0.7H), 8.12-8.06 (m, 1H), 7.98-7.80 (m, 2.8H), 7.66-7.58 (m, 0.2H), 5.83 (bs, 0.1H), 5.61 (t, 0.2H), 5.40-4.54 (m, 0.9H), 4.53-4.40 (m, 0.8H), 4.02-3.70 (m, 1.42H), 3.66 (dd, 0.58H, J = 14.7 Hz and J = 5.2 Hz), 3.30-2.99 (m, 3H), 1.68 (s, 6H), 1.62 (s, 6H), 1.60 (s, 6H), 1.31 (s, 4.5H), 1.25 (s, 4.5H);
LC-MS: R_t = 4.45; m/z: 678 $[M+H]^+$.

To a solution of trifluoroacetic acid (4 ml) and dichloromethane (2 ml) was added the mixture of 2-(*tert*-butoxyoxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-(*tert*-butoxyoxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (78 mg, 0.12 mmol). The solution was stirred at room temperature for 24 hours. The solvent was then evaporated in vacuo, which afforded 50 mg (72 %) of the title compounds as a mixture of trifluoroacetates.

^{1}H-NMR (DMSO-d_6): δ 12.32 (s, 1H), 9.75-9.20 (m, 2H), 8.40 (t, 1H, J = 6.0 Hz), 8.22-8.02 (m, 3H), 5.03 (bs, 0.5H), 4.52 (d, 1H), 4.38-4.10 (m, 2H), 3.88 (bs, 0.5H), 3.70-3.64 (m, 0.5H), 3.44-3.34 (m, 0.5H), 3.20-2.90 (m, 2H).

LC-MS: R_t = 1.28 min, m/z: 466 $[M+H]^+$

EXAMPLE 112



7-(*R*)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-(*S*)-4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert* butyl ester (18.4 g, 75.6 mmol) and triethylamine (12.65 mL, 90.79 mmol) in tetrahydrofuran (50 mL) cooled to –20°C was added isobutylchloroformate (11.81 mL, 90.79 mmol) and the mixture was stirred for 10 min at –20°C before a 25 % solution of ammonia in water (100 mL) was added. The temperature was kept at -20°C for 30 min before the cooling bath was removed and the reaction mixture was allowed to reach room temperature and stirring was continued for another hour. The reaction mixture was extracted with ethyl acetate (6 x 50 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, Flash 40, ethyl acetate) to give 8.51 g (46 %) of 2-(*S*)-carbamoyl-4-oxo-piperidine-1-carboxylic acid 1-*tert*-butyl ester.

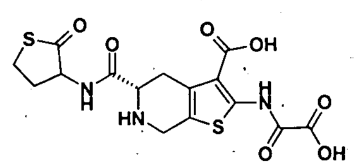
A solution of 2-(*S*)-carbamoyl-4-oxo-piperidine-1-carboxylic acid 1-*tert* butyl ester (3.51 g, 14.48 mmol), *tert*-butyl cyanoacetate (2.04 g, 14.48 mmol), sulphur (0.464 g, 14.48 mmol) and diisopropyl ethylamine (2.5 mL,

14.48 mmol) in methanol (20 mL) was heated 16 hours at 40°C under N_2. The volatiles were removed in vacuo and the residue was purified using column chromatography (SiO_2, Flash 40, petroleum ether/ethyl acetate 3:1) to give 1.33 g (23%) of a mixture 2-amino-5-(*S*)-carbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester and 2-amino-7-(*R*)-carbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester isomers.

0.5 g (1.25 mmol) of the above mixture was dissolved dichloromethane (10 mL) and imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (0.74 g, 3.77 mmol) and triethylamine (0.525 mL, 3.77 mmol) was added. The reaction mixture was stirred for 16 hours at room temperature before the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, Flash 40, petroleum ether/ethyl acetate (4:1)) too give 75 mg (11%) of 2-(*tert*-butoxyoxalyl-amino)-7-(*R*)-carbamoyl-4,7-dithydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester. This was dissolved in a mixture of trifluoacetic acid/dichloromethane (1:1) (10 mL) and stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was recrystallized from methanol to give 24 mg (39%) of the title compound.

LC-MS; R_t = 1.56 min, m/z: 314 $[M+H]^+$
Calculated for $C_{11}H_{11}N_3O_6S$, $0.25xC_2HF_3O_2$, $0.75xH_2O$
C, 38.88 %; H, 3.62 %; N, 11.83 %; Found:
C, 38.92 %; H, 3.92 %; N, 11.81 %.

EXAMPLE 113



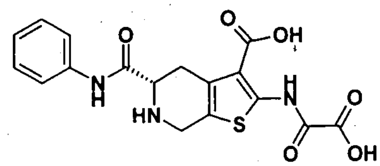
2-(Oxalyl-amino)-5-(*S*)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 2-amino-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,5-(*S*),6-tri-carboxylic acid 3,6-di-*tert*-butyl ester (0.30 g, 0.75 mmol) and triethylamine (0.21 mL, 1.51 mmol) in tetrahydrofuran (10 mL) was cooled to -20°C before isobutyl chloroformate (0.103 mL, 0.75 mmol) was added. The reaction mixture was stirred 15 min at -20°C before homocystein hydrochloride (116 mg, 0.75 mmol) was added. The cooling bath was removed and the reaction mixture was left for 16 hours at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography (SiO_2, Flash 40, heptane/ethyl acetate 2:1) to give 212 mg (56%) of 2-amino-5-(*S*)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester

A solution of 2-amino-5-(*S*)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (200 mg, 0.40 mmol), imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (235 mg, 1.20 mmol) and triethylamine (168 μL, 1.20 mmol) in dichloromethane (10 mL) was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, Flash 40, heptane/ethyl acetate 2:1) to give 250 mg (100%) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.
This was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1:1) (3 mL) and stirred for 16 hours at room temperature before diethyl ether (6 mL) was added. The precipitate was filtered off and washed with diethyl ether to give 172 mg (81%) of the title compound as a solid trifluoroacetate.

LC-MS; R_t = 0.41 min, m/z: 414 $[M+H]^+$
Calculated for $C_{15}H_{15}N_3O_7S_2$, $1.5xC_2HF_3O_2$, H_2O;
C, 35.88 %; H, 3.10 %; N, 6.97 %; Found:
C, 35.91 %; H, 3.54 %; N, 6.97 %.

EXAMPLE 114



2-(Oxalyl-amino)-5-(*S*)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

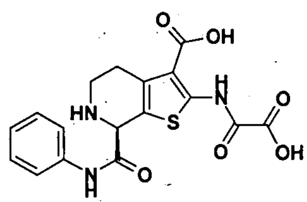
A solution of 2-amino-4,5,6,7-tetrahydro-thieno[2,3-*c*]-pyridine-3,5-(*S*),6-tricarboxylic acid 3,5-di-*tert*-butyl ester (300 mg, 0.75 mmol) and triethylamine (210 μL, 1.51 mmol) in tetrahydrofuran (10 mL) was cooled to -20°C before isobutylchloroformate (103 mg, 0.75 mmol) was introduced. The reaction mixture was stirred for 20 min before aniline (70 mg, 0.75 mmol) was added. The cooling bath was removed and the reaction was left for 16 hours at room temperature before the solvent was removed in vacuo. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (10 mL) and imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (443 mg, 2.26 mmol) and triethylamine (315 μL, 2.26 mmol) was added. The reaction mixture was stirred 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, Flash 40, heptane/ethyl acetate (3:1) to give 250 mg 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

2-(*tert*-Butoxyoxalyl-amino)-5-(*S*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1:1) (3 mL) and stirred for 16 hours at room temperature before diethyl ether (6 mL) was added. The precipitate was filtered off and washed with diethyl ether to give 155 mg (41%) of the title compound as a solid trifluoroacetate.

LC-MS; R_t = 0.86 min, m/z: 390 $[M+H]^+$

Calculated for $C_{17}H_{15}N_3O_6S$, $1.5xC_2HF_3O_2$, H_2O;
C, 41.53 %; H, 3.22 %; N, 7.26 %; Found:
C, 41.77 %; H, 3.29 %; N, 7.28 %.

EXAMPLE 115



2-(Oxalyl-amino)-7-(*R*)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-(*S*)-4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert* butyl ester (2.06 g, 8.47 mmol) and triethylamine (1.42 mL, 10.16 mmol) in tetrahydrofuran (20 mL) cooled to -20°C was added isobutylchloroformate (1.39 g, 10.16 mmol) and the mixture was stirred for 10 min at -20°C before aniline (946 mg, 10.16 mmol) was added. The cooling bath was removed and the reaction mixture was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was divided between water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with saturated sodium chloride (25 mL) and dried ($MgSO_4$). After filtration and concentration in vacuo the residue was purified using column chromatography (SiO_2, Flash 40, petroleum ether/ethyl acetate 5:1) to give 1.3 g (48%) of 4-oxo-2-(*S*)-phenyl-carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester.

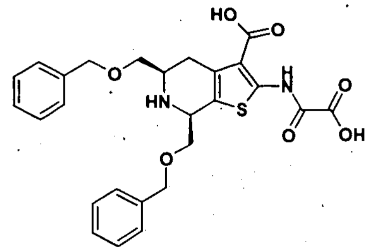
A solution of 4-oxo-2-(*S*)-phenylcarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.3 g, 4.08 mmol), *tert*-butylcyanoacetate (0.58 g, 4.08 mmol), sulphur (0.133 g, 4.08 mmol) and diisopropyl ethylamine (0.7 mL,

4.08 mmol) in methanol (10 mL) was heated under nitrogen to 40 °C for 16 hours before the solvent was removed in vacuo. The residue was subjected to column chromatography (SiO_2, Flash 40, petroleum ether/ethyl acetate 6:1) to give 0.70 g (36%) of a mixture of 2-amino-5-(*S*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester and 2-amino-7-(*R*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester isomers. The above mixture was dissolved in dichloromethane (20 mL) and imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (872 mg, 4.44 mmol) and triethylamine (618 μL, 4.44 mmol) was added. The reaction mixture was stirred 16 hours before the solvent was removed in vacuo and the residue was subjected to column chromatography (SiO_2, Flash 40, petroleum ether/ethyl acetate 5:1) to give 0.50 g (56%) as a mixture of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester and 2-(*tert*-butoxyoxalyl-amino)-7-(*R*)-phenylcarbamoyl-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester

300 mg of the mixture was dissolved in a mixture of trifluoacetic acid/dichloro-methane (1:1) (6.0 mL) and the solution was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified on preparative HPLC to give 70 mg (34%) of the title compound as a solid trifluoroacetate.

LC-MS; R_t = 0.95 min, m/z: 390 $[M+H]^+$
Calculated for $C_{17}H_{15}N_3O_6S$, $C_2HF_3O_2$, H_2O;
C, 43.77 %; H, 3.48 %; N, 8.06 %; Found:
C, 43.92 %; H, 3.44 %; N, 7.97 %.

EXAMPLE 116



5-(*R*),7-(*R*)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

Benzyloxyacetaldehyde (0.90 g; 6.0 mmol) and dimethyl (2-oxomethyl)phosphonate (1.0 g; 6.0 mmol) were dissolved in a mixture of tetrahydrofuran (25 ml) and water (20 ml). 1N Aqueous potassium hydroxide (6 ml) was added and the mixture was stirred for 30 min. Dichloromethane (50 ml) was added and the organic phase was separated, dried ($MgSO_4$) and evaporated in vacuo leaving 5-benzyloxypent-3-en-2-one.

^{1}H-NMR: 2.25 (s, 3H); 4.19 (dd, 2H); 4.55 (s, 2H); 6.34 (dt; 1H); 6.70 (dt, 1H); 7.26 (m, 5H).

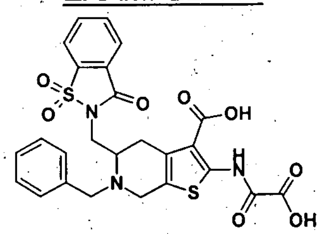
5-benzyloxypent-3-en-2-one was dissolved in methanol (5 ml) and ammonium acetate (13 mmol, 1.03 g) was mixted together with benzyloxyacetaldehyde (1.8 g; 12 mmol) and acetic acid (0.69 ml) and the mixture was stirred for 2 days. The solvent was removed in vacuo and the residue was chromatographed on silica using gradient elution from 100 % dichloromethane to 100 % ethyl acetate. A fraction (411 mg) contained (according to LC-MS; m/z 340.4) 2,5-di(benzyloxymethyl)-4-piperidone in an impure state was isolated. The crude mixture was dissolved in ethanol (3 ml) and *tert*-butylcyanoacetate (400 mg), sulfur (100 mg) and triethylamine was added and the mixture was stirred at room temperature overnight. The mixture was filtered and the solvent removed in vacuo. The residue was chromatographed on silica in a mixture of dichloromethane/(7% of 25% aqueous ammonia in ethanol) (40:1), which afforded 0.14 g of 2-amino-5-(*R*),7-(*R*)-bis-benzyloxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS: R_t: 6.03 min; m/z: 495.2 $[M+H]^+$

2-amino-5-(*R*),7-(*R*)-Bis-benzyloxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.14 g; 0.28 mmol) was dissolved in dichloromethane (5 ml) and treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.1 g; 0.5 mmol) and triethylamine (70 μl; 0.5 mmol), and stirred overnight, washed with water, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was chromatographed on silica using ethyl acetate/dichloromethane (1:3) as eluent. The residue was treated with trifluoroacetic acid (0.5 ml) in dichloromethane (0.5 ml) and stirred for 4 hours. Evaporation of the solvent in vacuo afforded 37 mg of the title compound.

LC-MS: R_t: 4.74 min; m/z: 511.4 $[M+H]^+$.

EXAMPLE 117



6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

1-Benzyl-4-oxo-piperidine-2-carboxylic acid ethyl ester (2.9 g; 11.1 mmol) (prepared in a similar way as described in "GENERAL CHIRAL SYNTHESIS" for 4-oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester using benzylamine instead of 1-(*S*)-phenethylamine) was dissolved in abs. ethanol (50 ml) and sulfur (0.35 g, 11.1 mmol), triethylamine (1.6 ml, 11.1 mmol), and *tert*-butylcyanoacetate (1.7 g, 11.1 mmol) were added and the mixture was stirred 2 days at room temperature. The solvent was removed in vacuo and the residue was chromatographed on silica using a mixture of ethyl actetate/heptane (1:4) as eleuent leaving a mixture (700 mg; 1:1 based on NMR) of 2-amino-6-benzyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,7-dicarboxylic acid 3-*tert*-butyl ester-7-ethyl ester and 2-amino-6-benzyl-4,5,6,7-tetrahydro-

thieno[2,3-c]pyridine-3,7-dicarboxylic acid 3-*tert*-butyl ester 5-ethyl ester which was used in the next step without separation. To this mixture was added tetrahydrofuran (5 ml) and lithium borohydride (1.1 ml of a 2M solution in tetrahydrofuran) and the mixture was stirred 18 hours. More lithium borohydride (5.0 ml of a 2M solution in tetrahydrofuran) was added and the mixture stirred for an additiona 4 days. Ethyl acetate (10 ml) was added dropwise and after 1 hour the mixture was poured onto water (100 ml) and extracted with dichloromethane (2 x 100 ml) and chromatographed on silica (using ethylacetate/heptane 1:1 as eluent), which afforded a mixture of 2-amino-6-benzyl-7-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester and 2-amino-6-benzyl-5-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (in total 187 mg). To this mixture was added dry tetrahydrofuran (10 ml), 2,3-dihydro-1,2-benzisothiazol-3-one-1,1-dioxide (100 mg; 0.55 mmol), triphenylphosphine (144 mg 0.55 mmol) and the mixture was cooled with ice. Diethyl azodicarboxylate (86 μl) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated <u>in</u> <u>vacuo</u> and the residue was chromatographed on silica using a mixture of ethyl acetate/heptane (1:1) as eluent leaving 94 mg of 2-amino-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR: (CDCl3): 1.52 (s, 9H); 2.75 (dd, 1H); 2.90 (dd, 1H); 3.55 (d, 1H); 3.72 (m, 4H); 3.94 (d, 1H); 4.12 (d, 1H); 5.97 (s, 2H); 7.14-7.37 (m, 5H); 7.80-8.03 (m, 4H).

LC-MS: R_t 5.47 min, m/z: 540.4 $[M+H]^+$

2-Amino-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (94 mg; 0.17 mmol) was dissolved in dichloromethane (5 ml) and treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.07 g; 0.3 mmol) and triethylamine (49 μl; 0.3 mmol), and stirred overnight, washed with water, 1N aqueous citric acid, dried ($MgSO_4$) and the solvent

removed in vacuo leaving 104 mg of 2-(*tert*-butoxyoxalyl-amino)-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil. LC-MS : R_t : 5.50 min, m/z: 668.6 $[M+H]^+$

2-(*tert*-Butoxyoxalyl-amino)-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (100 mg; 0.15 mmol) was treated with trifluoroacetic acid (1 m) in dichloromethane (4 ml) and stirred for 2 days. Evaporation of the solvent in vacuo afforded 90 mg of the title compound as a solid trifluoroacetate.

Calc. for $C_{25}H_{21}N_3O_8S_2$, $1.5xC_2HF_3O_2$, $0.5xH_2O$

C, 45.72%; H, 3.22%; N, 5.71%. Found:

C, 45.48%; H, 3.46%; N, 5.72%

LC-MS: R_t: 4.16 min; m/z: 556.2 $[M+H]^+$

EXAMPLE 118

Crystallisation of protein and protein-inhibitor complexes

Co-crystallization of PTP1B with inhibitors;

A 6-10 mg/ml preparation of PTP1B in 10 mM Tris pH 7.5, 25 mM NaCl, 0.2 mM EDTA and 3 mM DTT, was used for crystallization. Crystals were grown by the sitting as well as the hanging drop vapor diffusion methods. A 1:10 (PTP1B:inhibitor) molar ratio mixture was prepared at least one hour prior to crystallization. Two μl of PTP1B-inhibitor solution was mixed with 2 μl reservoir solution consisting of: 0.1 M Hepes buffer pH 7.5, 0.3-0.4 M Na-acetate or Mg-acetate, 12-16% Peg 8000 and/or 4% glycerol. The reservoir volume was 1 ml. Crystals grew to the size of 0.3-0.6X0.1-0.3X0.1-0.3 mm over 2-3 days.

Data collection.

All crystal data collections were performed at 100 K. The following cryo conditions were used: to the hanging or sitting drop 3 μl of 50% glycerol (containing 0.5 mmol inhibitor) were added. The crystal was removed from the drop after 5-30 min. and transferred to 50% glycerol (containing 0.5 mmol inhibitor) and rapidly flash frozen.

Data were collected using a mar345 image plate either at the MAX-lab synchrotron facilities in Lund (Sweden) or in-house equipped with a rotating anode (RU300) and Osmic multilayer mirror system. Typically a 1° oscillation was used for 60 images data sets in the resolution range 2.7-1.8 Å were obtained. The space group was determined to be P3121 for all crystals used.

Refinements.

As P3121 contains a polar axis and, thus, possesses more than one indexing possibility, a molecular replacement solution using Amore [ref] solution was found prior to the refinements. A high resolution PTP1B structure was used as a starting model, with ligand and water molecules omitted from the structure. All refinements were performed with Xplor. v. 3.851 [MSI]. Interchanging cycles of model building using X-build [MSI] and refinement were performed. The 2Fo-Fc maps were inspected by the use of X-ligand [MSI] at a 1.3 sigma level for densities that could correspond to the structures of the inhibitors. In all cases a well-suited inhibitor electron density was identified in the active site pocket, see figures 1-4. No other densities were identified to fit the inhibitors. Water molecules were inserted using the X-solvate program [MSI].

EXAMPLE 119

Coupling of 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid to Epoxy-activated Sepharose 6B.

This example describes the preparation of an immobilized compound suited for affinity chromatographic purification of PTPases (eg PTP1B or T-cell PTP).

3.5 g Epoxy-activated Sepharose 6B (Pharmacia Biotech) was prepared for coupling according to the manufacturers directions, and divided into 3 portions (3 x 8 ml gel-suspension, corresponding to 4 ml drained gel each).
8 ml portions of 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid dissolved to 10, 1 and 0.1 mM in a 0.2 M sodium carbonate coupling buffer pH 9 were mixed with the gel suspensions and agitated gently overnight at room temperature.
Exces ligand was washed away, the remaining active groups were blocked and the product was washed extensively at alternating pH, all according to the the manufacturers directions.
The products were stored refrigerated in 0.1 M acetate pH 4.0 containing 0.5 M sodium chloride.

Significant inhibition of PTP1B was demonstrated in the 20 µmole ligand/ml gel preparation, when diluted to 1 µl drained gel/ml.

EXAMPLE 120

Affinity purification of PTP1B using the compound 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid coupled to Epoxy-activated Sepharose 6B.

This example describes the affinity chromatographic purification of a PTPase.

2 ml of the product with 20 µmole ligand/ml described in example 55 was loaded into a 1.6 cm diameter column and equilibrated with a buffer (buffer A) containing

20 mM L-histidine
1 mM EDTA
7 mM Mercaptoethanol
100 mM Sodium chloride

and adjusted to pH 6.2 with 1 M HCl.

1.5 mg conventionally purified PTP1B in 5 ml buffer A, was applied to the column at 0.5 ml/min followed by a wash with 10 ml buffer A.

UV absorbing material without PTPase activity, corresponding to approx. 10 % of the totally applied material, passed through the column.

The flow direction was reversed, the flow increased to 2 ml/min and linear gradient elution started with a combined salt and pH gradient for 20 minutes using buffer B containing

20 mM L-histidine
1 mM EDTA
7 mM Mercaptoethanol
1 M Sodium chloride

and adjusted to pH 9.0 with 1 M NaOH.

Maximum elution took place at approx. 32 % buffer B (0.39 M NaCl and pH 6.8) in a broad peak.

The total activity yield in the elution peak was 70 %, and the specific activity of the enzyme was improved by a factor 1.4.

EXAMPLE 121

Use of compounds of the invention to identify substrates that are specifically dephosphorylated by PTPases that are inhibited by the compounds of the invention or by other PTPases.

The compounds of the invention are unique tools for identification of cellular substrates of the PTPases that are inhibited by the compounds of the invention. Substrates are herein defined as cellular proteins that (i) are phosphorylated on tyrosine residues, (ii) are dephosphorylated by PTPases that are inhibited by compounds of the invention or by other PTPases. If said substrates are dephosphorylated by PTPases that are inhibited by compounds of the invention, administration of the compounds of the invention will result in partial or total prevention of dephosphorylation of said substrates. As a result, a concomitant prolonged or increased activation may be observed of the signal transduction pathway (for definition, *vide infra*) in which said substrate is involved. Non-limiting examples of substrates are: the insulin receptor β subunit, IRS-1, IRS-2, IRS-3, IRS-4, JAK1, JAK2, shc-2, grb-2 (Hunter, *Cell 100:* 113-127 (2000)).

Importantly, the compounds of the invention can also be used to identify novel substrates. When the compounds of the invention have been used to identify the substrates of the PTPases that are inhibited by the compounds of the invention, a person skilled in the arts will be able to use this knowledge to establish animal models that will reflect a human condition or disease in which a compound of the invention will be indicated. Non-limiting example of the usefulness of said compounds of the invention will be in the following disease areas: diabetes, obesity cancer and conditions with unwarranted platelet aggregation.

To identify the substrates of the PTPases that are inhibited by the substrates of the invention the following methods may be employed. Whole animals and/or primary cells and/or cell lines that represent the

target organ or tissue may be used for these experiments. Non-limiting examples of animals are: *ob/*ob mice (worldwide web @ jax.org); *db/*db mice; Zucker obese rats. Non-limiting examples of target tissues or organs are: skeletal muscle, liver, adipose tissue, pancreas, the spleen, the bone marrow. Non-limiting examples of cell lines are: Chinese hamster ovary (CHO) cells (CHO-K1 – American Type Culture Collection (ATCC) Number CCL-61), Baby Hamster Kidney (BHK) cells (ATCC Number CRL-1632), HepG2 cells (ATCC Number HB-8065), C2C12 cells (ATCC Number CRL-1772), L6 cells (ATCC Number CRL-1458), RD cells (ATCC Number CCL-136). Said cells can either be unmanipulated or transfected transiently or permanently with plasmid vectors that encode proteins or substrates. Non-limiting example of a plasmid that allows expression in mammalian cells are: pcDNA1 and pcDNA3 (worldwode web @ invitrogen.com). Non-limiting examples of proteins or substrates that are transfected into said cell lines are: the insulin receptor, the IGF-I receptor, the EGF-R receptor, the PDGF receptor, IRS-1, IRS-2, IRS-3, IRS-4, p56Lck; Jak1, Jak2 (Hunter, *supra*).

The analysis consists of the following steps:

(A) stimulation of signal transduction pathways with and without the presence of the compounds of the invention. Signal transduction pathways are herein defined as a series of cellular processes that are initiated by a triggering event (such as stimulation of a tissue or cell by a hormone and/or a cytokine and/or cell-cell interaction and/or cell-cell substratum interaction) leading to various cellular effects including metabolic effects, cell differentiation and cell proliferation (Hunter, *supra*). Non-limiting examples of signal transduction pathways include: the insulin signaling pathway; the leptin signalling pathway; thrombin signalling pathway; the erythropoietin signaling pathway; the epidermal growth factor signaling pathway. Non-limiting examples of the effects of stimulating signal transduction pathways: glucose uptake; glycogen synthesis; cell proliferation; cell differentiation; platelet aggregation.

(B) Analysis and identification of substrates that show increased (or decreased) phosphorylation on tyrosine residues after administration of the compound of the invention in comparison with controls that did not receive the compound.

Step A. Stimulation of signal transduction pathways.

As a non-limiting example, insulin (concentration range: 0.1 to 100 nM, final concentration) is administered to primary hepatocytes in tissue culture plates. The compounds of the invention (concentration range: 10 nM to 100 μM) are administered to half of the plates, with the other plates acting as controls. The plates are incubated at 37 °C for various time periods: Typically for 0, 1, 2, 5, 15, 30 and 60 mins. Following this stimulation, the plates are treated as follows: The medium is rapidly aspirated and the cells washed twice with ice-cold PBS. Two milliliters of ice-cold lysis buffer (see below) is added and the plates are placed on ice for 2 minutes after which the cells are scraped off using a cell scraper ('rubber policeman'). The lysates are placed at 4 °C at a rotary shakerr. Dithiotreitol is added to a final concentration of 10 mM, and the lysates are centrifuged at 20,000 r.p.m.. Aliquots of the supernatants, i.e. lysates, are stored at –80 °C until further use.

Lysis buffer – for a total of 20 ml add the following

0.8 ml of 500 mM Tris-Cl, pH 7.4
0.2 ml of 100 mM EDTA
2.0 ml of 1 M NaCl
2.0 ml of 10 % (vol/vol) Triton X-100
80 μl of 250 mM PMSF
2 μl of 10 mg/ml aprotinin
20 μl of 1 mg/ml leupeptin
5 mM 100 mM iodoacetate
11.88 ml demineralized water

Step B. Analysis and identification of substrates that show increased (or decreased) phosphorylation on tyrosine residues after administration of the compound of the invention in comparison with controls that did not receive the compound.

As a non-limiting example, said lysates are subjected to two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) followed by detection of proteins that are phosphorylated on tyrosine residues (pTyr) by western blotting, techniques well-known to those skilled in the art (Marcus *et al. Electrophoresis 21*: 2622-2636 (2000)). Proteins that show increased (or decreased) pTyr are identified by comparing the western blots made from said lysates derived from said hepatocytes treated with both insulin and the compounds of the invention with said control lysates derived from said hepatocytes that were treated with insulin only. Increased pTyr of a protein shows that the said protein is regulated by the PTPase or PTPases that are inhibited by the compounds of the invention. Said protein may either be a direct substrate of the PTPase or PTPases that are inhibited by the compounds of the invention or the substrate of other PTPase(s) which activity is regulated by the PTPase or PTPases that are inhibited by the compounds of the invention. Decreased pTyr of a protein shows that said protein is the substrate of other PTPase(s) that is/are activated, directly or indirectly, by the PTPase or PTPases that are inhibited by the compounds of the invention. Having identified and visualized proteins, i.e. substrates, that show changed pTyr levels, the spots are cut out, digested with trypsin and analyzed by matrix assisted laser desorption/ionization-time of flight-mass spectrometry (MALDI-TOF-MS) (Marcus *et al.*, *supra*). To identify the nature of said substrate with changed pTyr levels the obtained mass fingerprints are analyzed as described by Marcus *et al.* (*supra*) or other methods well-known to those skilled in the art.

Said substrate can either be an already described protein or a novel protein. In both cases, the identification may be followed by cDNA cloning procedures with the aim of obtaining a full-length clone corresponding to said substrate using standard techniques well-known to those skilled in the art (Ausubel, F. M., *et al.* (ED.). Short Protocols in Molecular Biology, 2nd ed, John Wiley and Sons, inc., New York, ISBN 0-471-57735-9 (1992)). Said full-length clone may be expressed as recombinant proteins in prokaryotic or eukaryotic expression systems well-known to those skilled in the art (worldwide web @ invitrogen.com;

worldwide web @ stratagene.com; worldwide web @ promega.com), and the function of said substrate may in turn be studied both at the biochemical and cellular levels. Further, said recombinant proteins may further be used as an antigen to produce either polyclonal or monoclonal antibodies using techniques well-known to those skilled in the art. As a non-limiting example, with said full-length clone, said antibodies, and the compounds of the invention at hand, those skilled in the art will be able to study the tissue distribution and expression levels of said substrates in normal animals and animal models of diseases, such as diabetes, obesity, cancer and disturbances of platelet aggregation. A person skilled in the art will be able to use this knowledge to establish animal models or use already established animal models that will reflect a human condition or disease in which a compound of the invention will be indicated. Non-limiting example of the usefulness of said compounds of the invention will be in the following disease areas: diabetes, obesity, cancer and conditions with unwarranted platelet aggregation.

EXAMPLE 122

Identification of substrates that are dephosphorylated by PTPases that are inhibited by the compounds of the invention

The analysis consists of the following steps: (A) preparation of hyperphosphorylated substrates; (B) identification of said substrates that are dephosphorylated by PTPases that are dephosphorylated by compounds of the invention.

To identify the substrates of the PTPases that are inhibited by the compounds of the invention the following method may be employed. Primary cells and/or cell lines that represent the target organ or tissue may be used for these experiments. Non-limiting examples of target tissues or organs are: skeletal muscle, liver, adipose tissue, pancreas, the spleen, the bone marrow. Non-limiting examples of cell lines are: Chinese hamster ovary (CHO) cells (CHO-K1 – American Type Culture Collection (ATCC) Number CCL-61), Baby Hamster Kidney (BHK) cells (ATCC Number CRL-1632), HepG2 cells (ATCC Number HB-8065), C2C12 cells (ATCC

Number CRL-1772), L6 cells (ATCC Number CRL-1458), RD cells (ATCC Number CCL-136). Said cells can either be unmanipulated or transfected transiently or permanently with plasmid vectors that encode proteins or substrates. Non-limiting example of a plasmids that allow expression in mammalian cells are: pcDNA1 and pcDNA3 (worldwide web @ invitrogen.com). Non-limiting examples of proteins or substrates that are transfected into said cell lines are: the insulin receptor, the IGF-I receptor, the EGF-R receptor, the PDGF receptor, IRS-1, IRS-2, IRS-3, IRS-4, p56Lck; Jak1, Jak2 (Hunter, *supra*).

Step A

Said primary cells, tissues or cell lines are exposed to a general inhibitor of PTPases. This treatment results in induction of hyperphosphorylation of a multitude of cellular substrates. A non-limiting example of a general PTPase inhibitor is bisperoxovanadium 1,10 phenanthroline (bpV(phen)) (Posner *et al. J. Biol. Chem. 269*: 4596-4604 (1994)).

A non-limiting example of a hyperphosphorylation protocol: CHO cells that stably overexpress the insulin receptor are grown in 15 cm Petri dishes to 80-90 percent confluence (using F-12 medium with 10 percent fetal calf serum). The culture medium is replaced with medium that does not contain calf serum and are grown for additional 2 hrs at 37 °C. The plates are washed twice with phosphate buffered saline (PBS) and incubated for further 2 hours with 100 μM bpV(phen) and 100 nM insulin (Novo Nordisk) (final assay concentrations). Following this stimulation the plates are treated as follows: The medium is rapidly aspirated and the cells washed twice with ice-cold PBS. Two milliliters of ice-cold lysis buffer (see below) is added and the plates are placed on ice for 2 minutes after which the cells are scraped off using a cell scraper ('rubber policeman'). The lysates are placed at 4 °C at a rotary shaker for 1 hour. Dithiotreitol is added to a final concentration of 10 mM, and the lysates are centrifuged for 10 minutes at 20,000 r.p.m.. Aliquots of the supernatants, i.e. lysates, are stored at –80 °C until further use.

Lysis buffer – for a total of 20 ml add the following:

0.8 ml of 500 mM Tris-Cl, pH 7.4
0.2 ml of 100 mM EDTA
2.0 ml of 1 M NaCl
2.0 ml of 10 % (vol/vol) Triton X-100
80 μl of 250 mM PMSF
2 μl of 10 mg/ml aprotinin
20 μl of 1 mg/ml leupeptin
5 mM 100 mM iodoacetate
11.88 ml demineralized water

Step B

For these studies both novel and known PTPases may be used. The PTPases may be either isolated using the compounds of the invention as described in Example 120 or recombinant proteins. Non-limiting examples of known PTPases that are inhibited by compounds of the invention are PTP1B and TC-PTP. The cDNA for these PTPases are inserted in prokaryotic expression vectors and are expressed in *E. coli*. An overnight culture is diluted 1:25 into a total volume of 2 liters of SOB medium and grown at 37 °C for 3 hours. Isopropyl β-D-thiogalactoside (IPTG) is added to a final concentration of 0.1 mM, and the incubation is continued at room temperature for 3 hrs. The fusion proteins are purified according to the manufacturer's instructions (Amersham Pharmacia Biotech).

Aliquots of said lysates (60 μl) are mixed with said PTPase that is inhibited by said compound of the invention and incubated on ice for 1, 10, and 30 minutes. At each time point, 20 μl aliquots are removed and mixed with SDS loading buffer (20% (v/v) glycerol, 3% (w/v) SDS, 3% (v/v) 2-mercaptoethanol, 10 mM EDTA, 0.05% (w/v) bromphenol blue), heated at 100 °C for 2 minutes and stored at – 20 °C until use. Control lysates without addition of PTPase are treated identically.

As a non-limiting example, said lysates are subjected to two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) followed by detection of proteins that are phosphorylated on tyrosine residues (pTyr) by western blotting, techniques well-known to those skilled in the art (Marcus *et al.*

Electrophoresis 21: 2622-2636 (2000)). Proteins that show decreased pTyr are identified by comparing the western blots made from said lysates treated with said PTPase with said control lysates. Decreased pTyr of a protein shows that the said protein is a substrate of the PTPase or PTPases that are inhibited by the compounds of the invention. Having identified and visualized proteins, i.e. substrates, that show decreased pTyr levels, the spots are cut out, digested with trypsin and analyzed by matrix assisted laser desorption/ionization-time of flight-mass spectrometry (MALDI-TOF-MS) (Marcus *et al.*, *supra*). To identify the nature of said substrate with decreased pTyr levels the obtained mass fingerprints are analyzed as described by Marcus *et al.* (*supra*) or other methods well-known to those skilled in the art.

Said substrate can either be an already described protein or a novel protein. In both cases, the identification may be followed by cDNA cloning procedures with the aim of obtaining a full-length clone corresponding to said substrate using standard techniques well-know to those skilled in the art (Ausubel, F. M., *et al.* (ED.). Short protocols in molecular biology, 2nd ed, John Wiley and sons, inc., New York, ISBN 0-471-57735-9 (1992)). Further use of the knowledge include analysis in animal models as described in Example 59

EXAMPLE 123

Analysis for blood glucose lowering effects

The compounds of the invention are tested for blood glucose lowering effects in diabetic, obese female *ob/ob* mice. The mice are of similar age and body weights and they are randomized into groups of ten mice. They have free access to food and water during the experiment. The compounds are administered by either by gavage, subcutaneous, intravenous or intraperitoneal injections. The control group receives the same volume of vehicle as the mice that receive the compounds. Non-limiting examples of dose-range: 0.1, 0.3, 1.0, 3.0,10, 30, 100 mg per kg body weight. The blood glucose levels are measured two times before administration of the compounds of the invention and vehicle (to the control group). After administration of the compound, the blood glucose

levels are measured at the following time points: 1, 2, 4, 6, and 8 hours. A positive response is defined either as (i) a more than 25 percent reduction in blood glucose levels in the group receiving the compound of the invention compared to the group receiving the vehicle at any time point or (ii) statistically significant (i.e. $p<0.05$) reduction in the area under the blood glucose curve during the whole period (i.e. 8 hrs) in the group treated with the compounds of the invention compared to the group receiving the vehicle.

All documents cited herein are incorporated by reference in their entirety. In case of conflict in definitions, the present definitions control.

TABLE A

Table of the orthogonal three dimensional coordinates in Ångstroms and B factors (Å^2) for Protein Tyrosine Phosphatase 1B complexed with 2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid.

No	Amino acid		X	Y	Z	B
1	GLU	N	69.819	14.736	20.949	51.88
2	GLU	CA	69.381	16.070	20.592	50.12
3	GLU	C	68.816	16.123	19.177	50.96
4	GLU	O	69.477	15.855	18.147	47.57
5	GLU	CB	70.340	17.247	20.871	48.87
6	GLU	CG	69.694	18.607	20.512	43.78
7	GLU	CD	68.658	19.051	21.547	100.00
8	GLU	OE1	68.838	19.978	22.327	100.00
9	GLU	OE2	67.553	18.331	21.549	100.00
10	MET	N	67.550	16.476	19.190	38.96
11	MET	CA	66.810	16.619	18.000	33.41
12	MET	C	67.438	17.710	17.211	32.40
13	MET	O	67.335	17.745	16.010	34.44
14	MET	CB	65.376	17.042	18.345	34.94
15	MET	CG	65.321	18.129	19.414	36.89
16	MET	SD	63.595	18.598	19.738	37.03
17	MET	CE	63.053	17.127	20.689	35.19
18	GLU	N	68.060	18.625	17.893	31.60
19	GLU	CA	68.666	19.756	17.226	34.56
20	GLU	C	69.903	19.379	16.393	37.49
21	GLU	O	70.082	19.836	15.267	37.90
22	GLU	CB	68.955	20.859	18.236	36.57
23	GLU	CG	68.694	22.256	17.685	54.02
24	GLU	CD	68.602	23.271	18.792	84.59
25	GLU	OE1	68.338	22.965	19.970	60.30
26	GLU	OE2	68.826	24.499	18.340	56.97
27	LYS	N	70.740	18.506	16.928	34.63
28	LYS	CA	71.925	18.073	16.173	36.36
29	LYS	C	71.504	17.225	14.995	35.30
30	LYS	O	72.071	17.271	13.926	33.46
31	LYS	CB	72.858	17.280	17.069	44.20
32	LYS	CG	73.694	18.196	17.980	95.46
33	LYS	CD	74.837	17.496	18.729	100.00
34	LYS	CE	74.640	17.419	20.241	98.28
35	LYS	NZ	73.758	16.304	20.653	100.00
36	GLU	N	70.463	16.441	15.234	32.09
37	GLU	CA	69.894	15.573	14.227	31.58
38	GLU	C	69.285	16.367	13.096	33.03

39	GLU	O	69.380	16.076	11.917	33.46
40	GLU	CB	68.841	14.653	14.863	33.60
41	GLU	CG	67.823	14.152	13.814	51.32
42	GLU	CD	66.936	13.044	14.309	61.90
43	GLU	OE1	66.302	13.085	15.370	49.63
44	GLU	OE2	66.918	12.042	13.457	46.46
45	PHE	N	68.648	17.422	13.475	31.95
46	PHE	CA	68.008	18.269	12.488	32.19
47	PHE	C	69.072	18.712	11.539	37.60
48	PHE	O	68.928	18.630	10.309	32.52
49	PHE	CB	67.340	19.508	13.152	32.26
50	PHE	CG	66.508	20.348	12.196	30.98
51	PHE	CD1	65.161	20.064	11.967	29.63
52	PHE	CD2	67.094	21.402	11.499	29.81
53	PHE	CE1	64.398	20.834	11.096	31.86
54	PHE	CE2	66.354	22.185	10.621	32.68
55	PHE	CZ	65.004	21.896	10.423	34.10
56	GLU	N	70.164	19.160	12.179	36.63
57	GLU	CA	71.310	19.627	11.440	36.44
58	GLU	C	71.889	18.598	10.519	37.22
59	GLU	O	72.034	18.827	9.312	41.43
60	GLU	CB	72.309	20.346	12.308	40.39
61	GLU	CG	71.810	21.794	12.529	71.18
62	GLU	CD	71.946	22.266	13.953	100.00
63	GLU	OE1	72.735	21.752	14.751	100.00
64	GLU	OE2	71.139	23.288	14.223	100.00
65	GLN	N	72.140	17.413	11.024	31.25
66	GLN	CA	72.622	16.443	10.091	30.97
67	GLN	C	71.717	16.227	8.911	37.58
68	GLN	O	72.187	16.205	7.798	35.23
69	GLN	CB	72.828	15.118	10.746	32.09
70	GLN	CG	73.907	15.196	11.804	59.96
71	GLN	CD	74.286	13.786	12.123	100.00
72	GLN	OE1	73.653	12.854	11.579	100.00
73	GLN	NE2	75.309	13.631	12.975	100.00
74	ILE	N	70.403	16.026	9.164	37.32
75	ILE	CA	69.439	15.745	8.091	33.95
76	ILE	C	69.451	16.857	7.112	35.04
77	ILE	O	69.497	16.713	5.871	32.60
78	ILE	CB	68.007	15.516	8.591	33.88
79	ILE	CG1	67.983	14.281	9.450	33.37
80	ILE	CG2	67.062	15.263	7.427	27.69
81	ILE	CD1	66.734	14.241	10.340	41.16
82	ASP	N	69.392	17.990	7.705	31.68
83	ASP	CA	69.374	19.138	6.893	34.74
84	ASP	C	70.643	19.193	6.028	45.86

85	ASP	O	70.614	19.383	4.778 46.01
86	ASP	CB	69.131	20.360	7.773 36.60
87	ASP	CG	67.950	21.114	7.297 41.28
88	ASP	OD1	67.080	20.557	6.700 43.16
89	ASP	OD2	67.978	22.408	7.544 44.81
90	LYS	N	71.777	19.003	6.699 41.67
91	LYS	CA	73.008	19.033	5.954 43.82
92	LYS	C	73.035	17.928	4.864 46.27
93	LYS	O	73.357	18.177	3.709 45.13
94	LYS	CB	74.246	19.032	6.859 48.59
95	LYS	CG	74.736	17.622	7.242 93.12
96	LYS	CD	75.455	17.518	8.604 100.00
97	LYS	CE	76.327	16.267	8.797 100.00
98	LYS	NZ	75.740	15.262	9.683 100.00
99	SER	N	72.692	16.706	5.240 40.90
100	SER	CA	72.713	15.593	4.309 41.87
101	SER	C	71.575	15.604	3.324 48.03
102	SER	O	71.464	14.678	2.502 46.24
103	SER	CB	72.726	14.225	4.998 47.13
104	SER	OG	72.148	14.254	6.292 62.32
105	GLY	N	70.729	16.629	3.441 45.84
106	GLY	CA	69.560	16.743	2.595 46.85
107	GLY	C	68.809	15.410	2.577 51.28
108	GLY	O	68.437	14.883	1.532 56.29
109	SER	N	68.578	14.814	3.724 41.13
110	SER	CA	67.894	13.545	3.650 37.67
111	SER	C	66.529	13.420	4.344 33.83
112	SER	O	66.192	12.328	4.793 32.66
113	SER	CB	68.822	12.442	4.043 39.40
114	SER	OG	69.368	12.791	5.268 49.16
115	TRP	N	65.719	14.495	4.371 28.03
116	TRP	CA	64.390	14.413	4.947 24.69
117	TRP	C	63.521	13.375	4.242 30.79
118	TRP	O	62.773	12.639	4.915 30.44
119	TRP	CB	63.700	15.754	4.922 24.38
120	TRP	CG	64.317	16.654	5.925 24.63
121	TRP	CD1	65.208	17.670	5.685 27.42
122	TRP	CD2	64.101	16.581	7.359 22.65
123	TRP	NE1	65.553	18.274	6.893 27.47
124	TRP	CE2	64.916	17.588	7.946 28.99
125	TRP	CE3	63.346	15.749	8.195 21.13
126	TRP	CZ2	64.926	17.778	9.345 24.85
127	TRP	CZ3	63.385	15.932	9.554 20.43
128	TRP	CH2	64.168	16.938	10.115 21.06
129	ALA	N	63.620	13.268	2.876 26.09
130	ALA	CA	62.799	12.286	2.153 24.22

131	ALA	C	63.096	10.865	2.571	28.29
132	ALA	O	62.214	10.029	2.737	27.06
133	ALA	CB	62.920	12.477	0.652	25.69
134	ALA	N	64.363	10.580	2.794	26.20
135	ALA	CA	64.704	9.238	3.195	26.43
136	ALA	C	64.197	8.932	4.602	31.50
137	ALA	O	63.581	7.885	4.927	27.14
138	ALA	CB	66.210	9.022	3.107	26.43
139	ILE	N	64.482	9.876	5.467	28.04
140	ILE	CA	64.042	9.728	6.826	25.50
141	ILE	C	62.562	9.449	6.863	27.81
142	ILE	O	62.053	8.525	7.520	28.96
143	ILE	CB	64.267	11.063	7.477	28.83
144	ILE	CG1	65.751	11.246	7.430	30.75
145	ILE	CG2	63.815	11.019	8.941	29.55
146	ILE	CD1	66.368	10.532	8.621	40.82
147	TYR	N	61.873	10.317	6.156	25.16
148	TYR	CA	60.436	10.229	6.111	24.00
149	TYR	C	59.987	8.882	5.562	28.75
150	TYR	O	59.127	8.228	6.160	24.95
151	TYR	CB	59.814	11.445	5.419	23.47
152	TYR	CG	58.290	11.319	5.304	24.07
153	TYR	CD1	57.449	11.372	6.424	25.26
154	TYR	CD2	57.674	11.154	4.064	24.94
155	TYR	CE1	56.060	11.231	6.357	22.60
156	TYR	CE2	56.279	11.044	3.962	24.32
157	TYR	CZ	55.470	11.103	5.101	22.19
158	TYR	OH	54.112	11.014	4.979	21.43
159	GLN	N	60.604	8.446	4.440	26.68
160	GLN	CA	60.271	7.134	3.869	25.28
161	GLN	C	60.553	6.006	4.861	26.17
162	GLN	O	59.857	4.992	4.963	26.54
163	GLN	CB	61.021	6.871	2.543	27.78
164	GLN	CG	62.409	6.217	2.796	84.03
165	GLN	CD	63.607	6.501	1.839	100.00
166	GLN	OE1	64.737	6.062	2.164	98.42
167	GLN	NE2	63.414	7.188	0.676	76.48
168	ASP	N	61.596	6.176	5.640	24.54
169	ASP	CA	61.862	5.128	6.590	28.47
170	ASP	C	60.721	4.997	7.550	29.84
171	ASP	O	60.290	3.884	7.886	28.51
172	ASP	CB	63.220	5.284	7.314	35.64
173	ASP	CG	64.331	5.565	6.310	80.96
174	ASP	OD1	64.144	5.579	5.099	89.73
175	ASP	OD2	65.510	5.815	6.842	91.88
176	ILE	N	60.210	6.141	7.974	24.27

177	ILE	CA	59.060	6.052	8.889	24.52
178	ILE	C	57.903	5.367	8.255	24.70
179	ILE	O	57.252	4.522	8.841	25.35
180	ILE	CB	58.619	7.415	9.401	27.95
181	ILE	CG1	59.610	7.838	10.487	28.44
182	ILE	CG2	57.225	7.315	9.999	23.89
183	ILE	CD1	59.930	9.302	10.343	27.02
184	ARG	N	57.646	5.725	7.020	22.44
185	ARG	CA	56.511	5.098	6.330	22.70
186	ARG	C	56.702	3.601	6.226	26.26
187	ARG	O	55.761	2.788	6.333	23.08
188	ARG	CB	56.366	5.662	4.905	27.59
189	ARG	CG	55.825	7.104	4.773	27.34
190	ARG	CD	55.228	7.330	3.376	30.48
191	ARG	NE	54.182	8.369	3.362	86.57
192	ARG	CZ	53.614	8.942	2.268	100.00
193	ARG	NH1	53.954	8.615	1.006	100.00
194	ARG	NH2	52.685	9.890	2.445	33.19
195	HIS	N	57.967	3.235	5.974	26.18
196	HIS	CA	58.297	1.840	5.840	28.26
197	HIS	C	57.980	0.991	7.099	30.43
198	HIS	O	57.474	-0.179	7.075	22.68
199	HIS	CB	59.770	1.728	5.431	32.89
200	HIS	CG	60.149	0.296	5.206	42.37
201	HIS	ND1	60.626	-0.504	6.250	47.99
202	HIS	CD2	60.082	-0.474	4.078	47.47
203	HIS	CE1	60.816	-1.726	5.745	48.95
204	HIS	NE2	60.502	-1.747	4.449	48.75
205	GLU	N	58.321	1.588	8.255	30.06
206	GLU	CA	58.143	0.866	9.524	28.09
207	GLU	C	56.806	1.041	10.196	27.30
208	GLU	O	56.503	0.399	11.193	27.94
209	GLU	CB	59.244	1.273	10.531	30.97
210	GLU	CG	60.629	1.547	9.904	54.48
211	GLU	CD	61.444	2.586	10.685	100.00
212	GLU	OE1	61.742	2.444	11.872	100.00
213	GLU	OE2	61.812	3.644	9.973	100.00
214	ALA	N	55.999	1.936	9.673	21.78
215	ALA	CA	54.703	2.217	10.276	19.05
216	ALA	C	53.882	0.959	10.372	26.56
217	ALA	O	53.939	0.125	9.462	25.40
218	ALA	CB	53.944	3.236	9.423	20.42
219	SER	N	53.081	0.847	11.465	21.44
220	SER	CA	52.234	-0.307	11.732	19.39
221	SER	C	51.225	-0.517	10.663	27.89
222	SER	O	50.657	0.440	10.137	25.51

223	SER	CB	51.412	-0.049	12.974	21.80
224	SER	OG	52.257	0.317	14.021	26.89
225	ASP	N	50.935	-1.779	10.428	27.10
226	ASP	CA	49.936	-2.129	9.448	29.07
227	ASP	C	48.895	-2.997	10.125	30.02
228	ASP	O	49.166	-4.133	10.484	31.00
229	ASP	CB	50.631	-2.786	8.250	33.50
230	ASP	CG	49.690	-3.348	7.216	50.19
231	ASP	OD1	48.519	-3.040	7.156	46.03
232	ASP	OD2	50.278	-4.185	6.378	67.71
233	PHE	N	47.737	-2.422	10.384	20.70
234	PHE	CA	46.675	-3.127	11.085	19.53
235	PHE	C	45.446	-3.117	10.216	25.93
236	PHE	O	45.307	-2.281	9.357	28.17
237	PHE	CB	46.339	-2.422	12.436	19.46
238	PHE	CG	47.428	-2.504	13.514	18.83
239	PHE	CD1	47.752	-3.720	14.138	19.35
240	PHE	CD2	48.062	-1.346	13.989	17.72
241	PHE	CE1	48.753	-3.782	15.118	19.95
242	PHE	CE2	49.088	-1.384	14.939	21.08
243	PHE	CZ	49.410	-2.611	15.530	20.14
244	PRO	N	44.534	-4.031	10.446	23.52
245	PRO	CA	43.331	-4.115	9.640	21.50
246	PRO	C	42.303	-3.001	9.968	23.90
247	PRO	O	42.217	-2.497	11.117	22.13
248	PRO	CB	42.675	-5.448	10.030	22.86
249	PRO	CG	43.276	-5.845	11.381	29.00
250	PRO	CD	44.623	-5.147	11.450	24.62
251	CYS	N	41.517	-2.717	8.941	19.44
252	CYS	CA	40.442	-1.753	8.931	21.26
253	CYS	C	39.268	-2.405	8.253	24.35
254	CYS	O	38.706	-1.890	7.289	23.90
255	CYS	CB	40.832	-0.547	8.032	24.83
256	CYS	SG	42.442	0.202	8.391	31.37
257	ARG	N	38.910	-3.578	8.709	21.13
258	ARG	CA	37.877	-4.281	8.029	19.87
259	ARG	C	36.558	-3.582	8.150	24.13
260	ARG	O	35.758	-3.569	7.221	22.22
261	ARG	CB	37.842	-5.706	8.532	29.48
262	ARG	CG	36.735	-5.804	9.576	76.36
263	ARG	CD	36.827	-7.051	10.450	94.77
264	ARG	NE	36.033	-6.953	11.671	78.60
265	ARG	CZ	34.718	-6.843	11.637	91.25
266	ARG	NH1	34.073	-6.801	10.466	65.21
267	ARG	NH2	34.032	-6.768	12.785	88.97
268	VAL	N	36.307	-2.961	9.284	19.02

269	VAL	CA	35.034	-2.288	9.372	17.46	
270	VAL	C	34.925	-1.135	8.397	21.91	
271	VAL	O	33.923	-0.950	7.725	25.41	
272	VAL	CB	34.726	-1.775	10.740		17.65
273	VAL	CG1	33.338	-1.205	10.712		17.50
274	VAL	CG2	34.778	-2.908	11.719		19.97
275	ALA	N	35.964	-0.367	8.277	17.06	
276	ALA	CA	35.933	0.744	7.364	17.17	
277	ALA	C	35.664	0.295	5.949	26.79	
278	ALA	O	35.129	1.038	5.135	23.44	
279	ALA	CB	37.320	1.378	7.356	16.97	
280	LYS	N	36.118	-0.899	5.645	21.85	
281	LYS	CA	35.993	-1.403	4.299	23.03	
282	LYS	C	34.718	-2.121	4.012	26.65	
283	LYS	O	34.497	-2.565	2.898	29.21	
284	LYS	CB	37.201	-2.228	3.868	28.38	
285	LYS	CG	38.442	-1.359	3.651	30.93	
286	LYS	CD	38.066	-0.075	2.926	50.71	
287	LYS	CE	39.121	0.512	1.999	52.15	
288	LYS	NZ	38.518	1.459	1.033	53.44	
289	LEU	N	33.855	-2.250	4.983	26.04	
290	LEU	CA	32.594	-2.885	4.664	24.42	
291	LEU	C	31.830	-2.075	3.603	30.28	
292	LEU	O	31.830	-0.856	3.588	26.94	
293	LEU	CB	31.754	-2.820	5.907	25.29	
294	LEU	CG	31.721	-4.091	6.733	31.05	
295	LEU	CD1	32.743	-5.118	6.282	30.64	
296	LEU	CD2	31.726	-3.789	8.213	25.61	
297	PRO	N	31.131	-2.743	2.705	33.21	
298	PRO	CA	30.345	-2.081	1.660	32.26	
299	PRO	C	29.470	-0.982	2.155	29.80	
300	PRO	O	29.435	0.086	1.598	28.50	
301	PRO	CB	29.358	-3.139	1.155	35.94	
302	PRO	CG	29.790	-4.443	1.815	42.24	
303	PRO	CD	31.159	-4.194	2.448	36.58	
304	LYS	N	28.732	-1.278	3.191	29.93	
305	LYS	CA	27.805	-0.291	3.727	29.87	
306	LYS	C	28.449	1.003	4.192	32.15	
307	LYS	O	27.751	2.019	4.352	29.62	
308	LYS	CB	26.915	-0.840	4.835	28.99	
309	LYS	CG	27.683	-1.496	5.963	32.04	
310	LYS	CD	26.911	-1.359	7.260	40.42	
311	LYS	CE	27.142	-2.452	8.303	54.33	
312	LYS	NZ	26.267	-2.273	9.466	72.90	
313	ASN	N	29.760	0.960	4.440	25.44	
314	ASN	CA	30.439	2.153	4.930	24.36	

315	ASN	C	31.136	2.942	3.817	25.64
316	ASN	O	31.853	3.900	4.038	22.73
317	ASN	CB	31.454	1.740	6.025	21.85
318	ASN	CG	30.756	1.221	7.234	27.10
319	ASN	OD1	29.741	1.774	7.597	21.43
320	ASN	ND2	31.308	0.206	7.912	22.00
321	LYS	N	30.958	2.531	2.601	23.30
322	LYS	CA	31.685	3.175	1.546	23.68
323	LYS	C	31.498	4.684	1.542	26.11
324	LYS	O	32.434	5.476	1.385	22.38
325	LYS	CB	31.187	2.608	0.225	26.88
326	LYS	CG	32.036	2.987	-0.968	54.66
327	LYS	CD	32.007	1.947	-2.079	92.45
328	LYS	CE	31.689	2.503	-3.474	100.00
329	LYS	NZ	31.185	1.538	-4.438	100.00
330	ASN	N	30.233	5.068	1.662	22.80
331	ASN	CA	29.878	6.469	1.650	21.26
332	ASN	C	30.177	7.203	2.973	24.59
333	ASN	O	29.802	8.367	3.135	21.48
334	ASN	CB	28.430	6.739	1.159	19.81
335	ASN	CG	27.389	6.329	2.191	32.17
336	ASN	OD1	27.700	5.966	3.344	25.99
337	ASN	ND2	26.147	6.335	1.765	32.33
338	ARG	N	30.877	6.548	3.904	20.39
339	ARG	CA	31.241	7.201	5.150	18.64
340	ARG	C	32.702	7.535	5.136	20.09
341	ARG	O	33.225	8.042	6.113	20.82
342	ARG	CB	30.866	6.366	6.369	15.80
343	ARG	CG	29.337	6.275	6.511	24.13
344	ARG	CD	28.894	5.471	7.752	21.03
345	ARG	NE	27.448	5.428	7.873	21.48
346	ARG	CZ	26.841	5.336	9.030	28.21
347	ARG	NH1	27.509	5.294	10.182	18.63
348	ARG	NH2	25.519	5.288	9.033	23.12
349	ASN	N	33.389	7.218	4.039	18.29
350	ASN	CA	34.816	7.469	3.950	17.44
351	ASN	C	35.125	8.452	2.881	20.28
352	ASN	O	34.710	8.264	1.761	19.07
353	ASN	CB	35.593	6.181	3.663	15.55
354	ASN	CG	35.466	5.220	4.807	17.95
355	ASN	OD1	35.682	5.568	5.952	17.27
356	ASN	ND2	35.117	3.964	4.489	18.68
357	ARG	N	35.848	9.504	3.241	17.03
358	ARG	CA	36.149	10.550	2.276	16.04
359	ARG	C	37.140	10.084	1.227	21.28
360	ARG	O	37.000	10.388	0.049	17.65

361	ARG	CB	36.633	11.840	2.983	13.55
362	ARG	CG	37.024	12.938	2.016	13.76
363	ARG	CD	37.420	14.200	2.774	16.51
364	ARG	NE	36.224	14.791	3.392	18.16
365	ARG	CZ	35.306	15.542	2.703	26.85
366	ARG	NH1	35.365	15.811	1.381	20.84
367	ARG	NH2	34.234	16.012	3.341	16.64
368	TYR	N	38.164	9.354	1.679	17.86
369	TYR	CA	39.233	8.872	0.832	15.41
370	TYR	C	39.411	7.359	0.980	22.83
371	TYR	O	39.443	6.781	2.075	16.42
372	TYR	CB	40.562	9.498	1.157	14.29
373	TYR	CG	40.539	11.006	1.106	18.83
374	TYR	CD1	40.543	11.605	-0.152	18.23
375	TYR	CD2	40.543	11.799	2.270	17.14
376	TYR	CE1	40.467	12.989	-0.282	17.99
377	TYR	CE2	40.519	13.195	2.150	16.12
378	TYR	CZ	40.508	13.767	0.872	18.16
379	TYR	OH	40.491	15.147	0.711	18.89
380	ARG	N	39.483	6.735	-0.189	21.95
381	ARG	CA	39.577	5.315	-0.261	21.42
382	ARG	C	40.844	4.775	0.390	18.55
383	ARG	O	40.869	3.647	0.838	20.34
384	ARG	CB	39.306	4.858	-1.720	21.50
385	ARG	CG	40.427	4.051	-2.346	62.10
386	ARG	CD	41.233	4.684	-3.494	83.64
387	ARG	NE	42.611	4.161	-3.438	100.00
388	ARG	CZ	43.771	4.841	-3.523	100.00
389	ARG	NH1	43.842	6.149	-3.796	52.01
390	ARG	NH2	44.910	4.155	-3.451	95.71
391	ASP	N	41.862	5.576	0.492	14.95
392	ASP	CA	43.082	5.093	1.065	15.39
393	ASP	C	43.336	5.554	2.490	20.93
394	ASP	O	44.434	5.386	3.007	20.89
395	ASP	CB	44.260	5.583	0.229	16.63
396	ASP	CG	44.232	7.082	0.082	22.24
397	ASP	OD1	43.217	7.738	0.070	21.30
398	ASP	OD2	45.394	7.561	-0.238	19.13
399	VAL	N	42.347	6.156	3.118	16.50
400	VAL	CA	42.521	6.606	4.512	15.25
401	VAL	C	41.410	6.066	5.346	14.75
402	VAL	O	40.238	6.504	5.271	14.44
403	VAL	CB	42.451	8.123	4.686	17.27
404	VAL	CG1	42.721	8.517	6.182	13.83
405	VAL	CG2	43.493	8.755	3.753	16.91
406	SER	N	41.767	5.113	6.158	15.99

407	SER	CA	40.760	4.485	6.993	17.42
408	SER	C	41.244	4.320	8.405	19.32
409	SER	O	42.424	4.173	8.656	18.77
410	SER	CB	40.514	3.028	6.484	22.19
411	SER	OG	40.054	3.029	5.131	21.85
412	PRO	N	40.292	4.229	9.316	17.04
413	PRO	CA	40.684	3.951	10.686	14.95
414	PRO	C	40.991	2.428	10.873	21.72
415	PRO	O	40.275	1.571	10.353	21.93
416	PRO	CB	39.423	4.252	11.548	14.87
417	PRO	CG	38.238	4.153	10.604	18.96
418	PRO	CD	38.800	4.338	9.177	15.06
419	PHE	N	42.019	2.096	11.691	19.00
420	PHE	CA	42.266	0.711	12.046	16.26
421	PHE	C	41.099	0.239	12.907	20.51
422	PHE	O	40.517	0.996	13.712	18.21
423	PHE	CB	43.484	0.629	12.972	16.62
424	PHE	CG	44.768	0.998	12.290	16.69
425	PHE	CD1	45.003	0.566	10.991	17.42
426	PHE	CD2	45.748	1.751	12.951	16.19
427	PHE	CE1	46.217	0.883	10.383	17.05
428	PHE	CE2	46.957	2.090	12.351	17.24
429	PHE	CZ	47.157	1.686	11.030	15.76
430	ASP	N	40.774	-1.056	12.819	19.69
431	ASP	CA	39.725	-1.541	13.645	19.38
432	ASP	C	40.050	-1.394	15.135	22.03
433	ASP	O	39.169	-1.155	15.966	20.90
434	ASP	CB	39.442	-3.033	13.331	21.07
435	ASP	CG	38.887	-3.204	11.964	26.66
436	ASP	OD1	38.132	-2.404	11.443	25.86
437	ASP	OD2	39.391	-4.217	11.336	29.95
438	HIS	N	41.288	-1.623	15.513	16.04
439	HIS	CA	41.509	-1.608	16.924	16.58
440	HIS	C	41.355	-0.281	17.634	25.32
441	HIS	O	41.100	-0.239	18.870	24.53
442	HIS	CB	42.856	-2.240	17.272	15.76
443	HIS	CG	44.037	-1.338	17.088	17.63
444	HIS	ND1	44.449	-0.441	18.079	19.17
445	HIS	CD2	44.890	-1.230	16.041	16.56
446	HIS	CE1	45.560	0.159	17.644	17.00
447	HIS	NE2	45.831	-0.298	16.427	17.69
448	SER	N	41.535	0.808	16.896	18.44
449	SER	CA	41.467	2.102	17.571	17.07
450	SER	C	40.307	2.966	17.101	24.02
451	SER	O	40.171	4.125	17.523	19.51
452	SER	CB	42.776	2.867	17.350	17.91

453	SER	OG	43.130	2.848	15.967	17.63
454	ARG	N	39.469	2.429	16.223	18.61
455	ARG	CA	38.403	3.278	15.711	17.44
456	ARG	C	37.438	3.714	16.763	21.37
457	ARG	O	37.179	2.969	17.729	21.12
458	ARG	CB	37.602	2.640	14.577	20.23
459	ARG	CG	36.621	1.515	15.009	21.54
460	ARG	CD	35.968	0.725	13.835	24.77
461	ARG	NE	34.948	-0.234	14.300	23.61
462	ARG	CZ	33.667	0.024	14.419	28.43
463	ARG	NH1	33.166	1.215	14.106	17.26
464	ARG	NH2	32.865	-0.945	14.886	22.24
465	ILE	N	36.814	4.891	16.529	20.42
466	ILE	CA	35.777	5.390	17.455	17.73
467	ILE	C	34.431	4.780	17.042	23.53
468	ILE	O	34.021	4.855	15.864	19.57
469	ILE	CB	35.640	6.925	17.449	18.61
470	ILE	CG1	36.949	7.648	17.816	16.90
471	ILE	CG2	34.493	7.340	18.369	19.54
472	ILE	CD1	37.390	7.446	19.280	23.50
473	LYS	N	33.724	4.181	18.014	17.77
474	LYS	CA	32.479	3.661	17.638	19.44
475	LYS	C	31.329	4.585	18.080	23.14
476	LYS	O	31.307	5.073	19.222	23.03
477	LYS	CB	32.343	2.312	18.288	25.11
478	LYS	CG	33.271	1.269	17.706	28.50
479	LYS	CD	32.904	-0.078	18.301	42.01
480	LYS	CE	34.060	-1.057	18.404	50.09
481	LYS	NZ	33.628	-2.377	18.900	65.13
482	LEU	N	30.358	4.822	17.187	19.37
483	LEU	CA	29.173	5.650	17.536	19.21
484	LEU	C	28.311	4.790	18.451	30.47
485	LEU	O	28.311	3.555	18.264	27.66
486	LEU	CB	28.346	5.917	16.283	18.17
487	LEU	CG	29.225	6.632	15.268	20.04
488	LEU	CD1	28.533	6.828	13.952	17.50
489	LEU	CD2	29.630	7.998	15.864	17.41
490	HIS	N	27.616	5.406	19.435	24.92
491	HIS	CA	26.790	4.616	20.333	23.96
492	HIS	C	25.439	4.506	19.717	34.63
493	HIS	O	24.491	5.195	20.064	38.67
494	HIS	CB	26.695	5.217	21.719	24.41
495	HIS	CG	28.030	5.381	22.372	29.98
496	HIS	ND1	28.197	6.121	23.570	33.91
497	HIS	CD2	29.258	4.908	21.994	31.10
498	HIS	CE1	29.504	6.052	23.881	33.12

499	HIS	NE2	30.159	5.332	22.951	32.31
500	GLN	N	25.367	3.685	18.712	38.08
501	GLN	CA	24.103	3.522	18.003	41.99
502	GLN	C	24.077	2.125	17.437	46.43
503	GLN	O	25.111	1.523	17.202	42.03
504	GLN	CB	23.751	4.631	16.958	43.94
505	GLN	CG	24.597	4.425	15.691	50.12
506	GLN	CD	24.204	5.284	14.508	78.89
507	GLN	OE1	24.235	6.526	14.622	72.88
508	GLN	NE2	23.934	4.636	13.354	62.05
509	GLU	N	22.876	1.603	17.293	50.52
510	GLU	CA	22.676	0.234	16.832	53.51
511	GLU	C	22.637	0.058	15.328	53.08
512	GLU	O	23.006	-0.999	14.825	48.73
513	GLU	CB	21.441	-0.418	17.510	56.24
514	GLU	CG	21.550	-0.429	19.051	74.99
515	GLU	CD	20.383	-1.136	19.705	100.00
516	GLU	OE1	19.203	-0.939	19.368	100.00
517	GLU	OE2	20.768	-2.009	20.636	100.00
518	ASP	N	22.170	1.083	14.619	50.94
519	ASP	CA	22.101	0.990	13.183	52.56
520	ASP	C	23.492	0.706	12.532	50.81
521	ASP	O	23.723	-0.285	11.795	54.32
522	ASP	CB	21.388	2.250	12.634	57.77
523	ASP	CG	21.808	2.668	11.243	94.02
524	ASP	OD1	21.577	1.977	10.250	99.87
525	ASP	OD2	22.439	3.847	11.214	100.00
526	ASN	N	24.444	1.597	12.808	34.60
527	ASN	CA	25.773	1.475	12.236	28.07
528	ASN	C	26.669	2.345	13.088	29.15
529	ASN	O	26.536	3.556	13.101	30.48
530	ASN	CB	25.734	2.022	10.803	19.62
531	ASN	CG	27.024	1.823	10.062	27.76
532	ASN	OD1	28.067	1.547	10.679	22.79
533	ASN	ND2	26.967	1.995	8.729	21.65
534	ASP	N	27.600	1.752	13.806	22.25
535	ASP	CA	28.430	2.534	14.667	20.02
536	ASP	C	29.676	3.124	14.011	22.15
537	ASP	O	30.575	3.603	14.710	22.95
538	ASP	CB	28.858	1.548	15.757	21.84
539	ASP	CG	29.803	0.461	15.282	26.22
540	ASP	OD1	30.328	0.421	14.195	26.63
541	ASP	OD2	30.146	-0.355	16.235	35.64
542	TYR	N	29.794	3.001	12.697	19.04
543	TYR	CA	31.033	3.440	12.034	16.92
544	TYR	C	31.184	4.931	11.701	22.03

545	TYR	O	30.325	5.601	11.107	22.84
546	TYR	CB	31.149	2.733	10.691	16.06
547	TYR	CG	32.412	3.169	9.987	17.61
548	TYR	CD1	33.645	2.670	10.425	20.91
549	TYR	CD2	32.403	4.043	8.886	16.20
550	TYR	CE1	34.857	3.065	9.828	19.50
551	TYR	CE2	33.596	4.460	8.282	13.17
552	TYR	CZ	34.818	3.973	8.769	14.97
553	TYR	OH	36.004	4.360	8.214	18.92
554	ILE	N	32.319	5.440	12.061	19.32
555	ILE	CA	32.752	6.780	11.682	17.75
556	ILE	C	34.257	6.676	11.366	16.65
557	ILE	O	35.022	5.912	11.984	14.78
558	ILE	CB	32.460	7.883	12.709	18.72
559	ILE	CG1	32.923	9.269	12.196	17.13
560	ILE	CG2	33.132	7.524	14.066	19.79
561	ILE	CD1	32.357	10.364	13.106	16.24
562	ASN	N	34.721	7.445	10.394	14.05
563	ASN	CA	36.134	7.408	10.072	12.04
564	ASN	C	36.861	8.263	11.062	18.49
565	ASN	O	37.028	9.462	10.808	16.53
566	ASN	CB	36.392	7.908	8.637	10.31
567	ASN	CG	37.806	7.615	8.161	18.51
568	ASN	OD1	38.803	7.928	8.840	17.25
569	ASN	ND2	37.914	7.096	6.948	13.86
570	ALA	N	37.206	7.670	12.215	15.81
571	ALA	CA	37.822	8.363	13.318	15.05
572	ALA	C	38.551	7.400	14.203	17.50
573	ALA	O	38.093	6.297	14.414	15.99
574	ALA	CB	36.768	9.111	14.121	15.21
575	SER	N	39.670	7.856	14.752	13.78
576	SER	CA	40.518	7.002	15.565	14.32
577	SER	C	40.915	7.650	16.857	16.94
578	SER	O	41.210	8.834	16.908	18.12
579	SER	CB	41.859	6.766	14.820	15.23
580	SER	OG	41.642	6.232	13.488	17.37
581	LEU	N	41.046	6.853	17.898	15.51
582	LEU	CA	41.503	7.396	19.161	15.13
583	LEU	C	43.015	7.175	19.229	22.22
584	LEU	O	43.454	6.029	19.128	21.68
585	LEU	CB	40.801	6.641	20.374	16.59
586	LEU	CG	41.333	6.988	21.784	19.94
587	LEU	CD1	41.053	8.438	22.118	20.86
588	LEU	CD2	40.611	6.204	22.847	21.37
589	ILE	N	43.797	8.247	19.421	17.07
590	ILE	CA	45.219	8.168	19.506	16.19

591	ILE	C	45.524	8.335	20.995	24.53
592	ILE	O	45.338	9.380	21.568	22.94
593	ILE	CB	45.845	9.330	18.796	18.65
594	ILE	CG1	45.927	9.229	17.286	18.37
595	ILE	CG2	47.265	9.378	19.290	21.51
596	ILE	CD1	44.791	8.564	16.611	25.42
597	LYS	N	45.955	7.285	21.664	20.46
598	LYS	CA	46.162	7.350	23.092	20.79
599	LYS	C	47.630	7.299	23.390	24.25
600	LYS	O	48.236	6.260	23.159	24.06
601	LYS	CB	45.396	6.160	23.699	24.07
602	LYS	CG	44.960	6.286	25.154	48.81
603	LYS	CD	44.128	5.081	25.617	70.96
604	LYS	CE	44.276	4.756	27.109	99.34
605	LYS	NZ	44.076	3.328	27.445	100.00
606	MET	N	48.201	8.455	23.822	22.51
607	MET	CA	49.625	8.581	24.124	20.07
608	MET	C	49.859	8.290	25.599	27.14
609	MET	O	49.758	9.141	26.462	24.51
610	MET	CB	50.266	9.882	23.647	19.62
611	MET	CG	50.032	10.097	22.162	21.13
612	MET	SD	50.570	8.761	21.081	23.27
613	MET	CE	52.316	9.093	21.055	18.81
614	GLU	N	50.136	7.023	25.830	28.15
615	GLU	CA	50.280	6.525	27.160	29.78
616	GLU	C	51.248	7.321	28.030	34.27
617	GLU	O	50.881	7.991	29.015	33.62
618	GLU	CB	50.621	5.054	27.058	30.77
619	GLU	CG	50.491	4.307	28.379	42.42
620	GLU	CD	50.541	2.833	28.160	86.17
621	GLU	OE1	51.464	2.282	27.586	100.00
622	GLU	OE2	49.454	2.226	28.584	100.00
623	GLU	N	52.506	7.246	27.649	30.68
624	GLU	CA	53.546	7.943	28.396	31.16
625	GLU	C	53.243	9.397	28.518	35.90
626	GLU	O	53.388	9.913	29.567	36.43
627	GLU	CB	54.865	7.737	27.681	33.02
628	GLU	CG	56.142	8.220	28.385	46.68
629	GLU	CD	57.242	8.086	27.353	78.67
630	GLU	OE1	57.023	7.823	26.163	59.52
631	GLU	OE2	58.437	8.258	27.835	84.75
632	ALA	N	52.800	10.068	27.441	34.48
633	ALA	CA	52.488	11.493	27.524	31.47
634	ALA	C	51.242	11.736	28.308	33.12
635	ALA	O	51.026	12.820	28.781	31.13
636	ALA	CB	52.294	12.082	26.132	31.22

637	GLN	N	50.354	10.764	28.383	32.47
638	GLN	CA	49.116	11.014	29.114	35.37
639	GLN	C	48.196	12.076	28.454	39.78
640	GLN	O	47.700	13.026	29.072	40.91
641	GLN	CB	49.434	11.386	30.560	39.09
642	GLN	CG	50.174	10.260	31.290	72.08
643	GLN	CD	49.157	9.374	31.957	100.00
644	GLN	OE1	48.700	9.687	33.092	100.00
645	GLN	NE2	48.738	8.341	31.206	99.83
646	ARG	N	47.979	11.913	27.140	28.50
647	ARG	CA	47.086	12.751	26.374	23.58
648	ARG	C	46.524	11.885	25.282	24.24
649	ARG	O	47.232	11.052	24.744	26.56
650	ARG	CB	47.779	13.904	25.722	23.27
651	ARG	CG	46.780	14.899	25.126	26.99
652	ARG	CD	47.361	16.299	24.960	26.70
653	ARG	NE	47.293	17.043	26.199	23.46
654	ARG	CZ	47.954	18.135	26.422	24.69
655	ARG	NH1	48.785	18.663	25.532	22.83
656	ARG	NH2	47.826	18.721	27.596	23.63
657	SER	N	45.249	12.005	25.019	19.60
658	SER	CA	44.632	11.302	23.912	18.87
659	SER	C	44.089	12.361	22.960	23.27
660	SER	O	43.869	13.515	23.332	20.11
661	SER	CB	43.455	10.478	24.343	21.80
662	SER	OG	43.930	9.552	25.250	30.13
663	TYR	N	43.820	11.959	21.724	21.22
664	TYR	CA	43.211	12.812	20.702	17.17
665	TYR	C	42.381	11.892	19.853	21.01
666	TYR	O	42.734	10.702	19.695	20.98
667	TYR	CB	44.261	13.337	19.707	18.74
668	TYR	CG	45.522	13.929	20.298	16.73
669	TYR	CD1	46.618	13.125	20.576	17.39
670	TYR	CD2	45.619	15.309	20.511	16.87
671	TYR	CE1	47.790	13.694	21.079	18.92
672	TYR	CE2	46.773	15.899	21.033	17.15
673	TYR	CZ	47.854	15.067	21.332	23.78
674	TYR	OH	49.001	15.602	21.876	23.03
675	ILE	N	41.328	12.435	19.274	17.07
676	ILE	CA	40.554	11.723	18.279	16.38
677	ILE	C	40.866	12.407	16.961	19.66
678	ILE	O	40.778	13.628	16.850	19.42
679	ILE	CB	39.027	11.735	18.509	21.59
680	ILE	CG1	38.653	10.894	19.775	21.73
681	ILE	CG2	38.255	11.292	17.209	19.23
682	ILE	CD1	37.204	11.104	20.239	19.35

683	LEU	N	41.336	11.645	16.006	15.32
684	LEU	CA	41.675	12.234	14.715	14.26
685	LEU	C	40.656	11.756	13.748	18.37
686	LEU	O	40.389	10.571	13.738	16.49
687	LEU	CB	43.066	11.848	14.198	13.33
688	LEU	CG	44.175	12.803	14.642	17.41
689	LEU	CD1	45.534	12.403	13.995	16.26
690	LEU	CD2	44.281	12.897	16.182	15.86
691	THR	N	40.050	12.645	12.963	14.18
692	THR	CA	39.024	12.145	12.076	13.33
693	THR	C	39.116	12.910	10.755	16.62
694	THR	O	39.788	13.946	10.696	15.02
695	THR	CB	37.644	12.338	12.815	15.01
696	THR	OG1	36.550	11.816	12.090	15.33
697	THR	CG2	37.396	13.829	13.035	11.94
698	GLN	N	38.432	12.417	9.692	15.62
699	GLN	CA	38.460	13.162	8.437	14.08
700	GLN	C	37.474	14.358	8.490	16.44
701	GLN	O	36.541	14.444	9.358	16.22
702	GLN	CB	38.017	12.224	7.323	13.86
703	GLN	CG	36.562	11.804	7.547	18.12
704	GLN	CD	35.915	10.847	6.544	19.07
705	GLN	OE1	34.655	10.690	6.513	19.98
706	GLN	NE2	36.756	10.142	5.818	11.61
707	GLY	N	37.556	15.222	7.487	15.42
708	GLY	CA	36.598	16.340	7.384	12.58
709	GLY	C	35.252	15.724	7.143	16.22
710	GLY	O	35.067	14.965	6.204	14.03
711	PRO	N	34.274	16.005	7.986	16.60
712	PRO	CA	32.950	15.389	7.745	15.78
713	PRO	C	32.405	15.529	6.317	20.52
714	PRO	O	32.677	16.525	5.642	19.37
715	PRO	CB	32.010	16.071	8.734	15.66
716	PRO	CG	32.902	16.749	9.800	17.67
717	PRO	CD	34.316	16.772	9.281	14.44
718	LEU	N	31.620	14.505	5.898	16.55
719	LEU	CA	30.962	14.416	4.631	14.43
720	LEU	C	29.522	14.909	4.834	22.58
721	LEU	O	29.029	14.985	5.933	20.15
722	LEU	CB	30.952	12.997	4.038	14.77
723	LEU	CG	32.352	12.481	3.728	18.92
724	LEU	CD1	32.333	10.957	3.798	20.45
725	LEU	CD2	32.799	12.968	2.329	19.10
726	PRO	N	28.852	15.291	3.742	23.61
727	PRO	CA	27.526	15.812	3.867	23.49
728	PRO	C	26.616	14.852	4.520	26.41

729	PRO	O	25.574	15.258	4.934	30.17
730	PRO	CB	27.017	16.030	2.454	25.04
731	PRO	CG	28.057	15.523	1.480	29.04
732	PRO	CD	29.290	15.276	2.312	23.33
733	ASN	N	26.973	13.586	4.607	21.62
734	ASN	CA	26.068	12.632	5.237	17.84
735	ASN	C	26.608	12.193	6.557	22.95
736	ASN	O	25.978	11.361	7.233	23.70
737	ASN	CB	25.861	11.386	4.362	18.60
738	ASN	CG	27.174	10.691	3.998	24.49
739	ASN	OD1	28.160	11.365	3.684	24.35
740	ASN	ND2	27.214	9.338	4.017	24.03
741	THR	N	27.791	12.714	6.939	16.40
742	THR	CA	28.325	12.237	8.220	15.19
743	THR	C	28.433	13.364	9.223	21.17
744	THR	O	29.095	13.234	10.219	19.70
745	THR	CB	29.694	11.529	8.112	18.74
746	THR	OG1	30.690	12.447	7.709	19.88
747	THR	CG2	29.683	10.379	7.103	16.93
748	CYS	N	27.783	14.491	8.970	16.82
749	CYS	CA	27.883	15.573	9.943	18.20
750	CYS	C	27.174	15.247	11.228	19.02
751	CYS	O	27.613	15.697	12.308	20.16
752	CYS	CB	27.325	16.925	9.410	19.21
753	CYS	SG	28.252	17.458	7.951	23.17
754	GLY	N	26.054	14.501	11.125	17.59
755	GLY	CA	25.352	14.185	12.370	16.40
756	GLY	C	26.210	13.222	13.189	18.70
757	GLY	O	26.279	13.293	14.394	18.52
758	HIS	N	26.865	12.306	12.499	17.15
759	HIS	CA	27.754	11.319	13.158	17.16
760	HIS	C	28.925	12.017	13.833	20.07
761	HIS	O	29.404	11.647	14.889	20.41
762	HIS	CB	28.393	10.342	12.120	18.16
763	HIS	CG	27.384	9.635	11.299	19.12
764	HIS	ND1	27.704	9.228	9.989	22.15
765	HIS	CD2	26.096	9.300	11.596	17.48
766	HIS	CE1	26.596	8.639	9.509	20.83
767	HIS	NE2	25.620	8.661	10.438	20.03
768	PHE	N	29.491	13.003	13.166	17.15
769	PHE	CA	30.592	13.729	13.736	15.25
770	PHE	C	30.214	14.331	15.139	22.13
771	PHE	O	30.894	14.098	16.171	21.51
772	PHE	CB	31.025	14.822	12.736	15.12
773	PHE	CG	32.096	15.740	13.307	14.74
774	PHE	CD1	31.746	16.887	14.020	15.97

775	PHE	CD2	33.466	15.466	13.140	15.95
776	PHE	CE1	32.734	17.739	14.539	16.67
777	PHE	CE2	34.475	16.298	13.663	17.69
778	PHE	CZ	34.095	17.428	14.398	14.91
779	TRP	N	29.096	15.088	15.168	19.55
780	TRP	CA	28.632	15.704	16.421	18.79
781	TRP	C	28.147	14.656	17.418	21.85
782	TRP	O	28.289	14.839	18.633	21.13
783	TRP	CB	27.576	16.758	16.169	16.67
784	TRP	CG	28.210	17.904	15.491	16.11
785	TRP	CD1	27.962	18.318	14.214	18.99
786	TRP	CD2	29.206	18.776	16.023	14.97
787	TRP	NE1	28.768	19.412	13.916	18.96
788	TRP	CE2	29.547	19.692	15.015	18.62
789	TRP	CE3	29.867	18.880	17.250	16.41
790	TRP	CZ2	30.506	20.686	15.213	17.94
791	TRP	CZ3	30.823	19.869	17.428	16.16
792	TRP	CH2	31.165	20.737	16.412	16.86
793	GLU	N	27.626	13.536	16.911	17.79
794	GLU	CA	27.268	12.489	17.811	16.48
795	GLU	C	28.499	12.004	18.561	20.28
796	GLU	O	28.480	11.817	19.780	18.97
797	GLU	CB	26.630	11.293	17.103	17.70
798	GLU	CG	26.576	10.108	18.107	18.51
799	GLU	CD	25.985	8.904	17.457	36.95
800	GLU	OE1	25.635	8.939	16.304	24.52
801	GLU	OE2	25.828	7.845	18.231	22.85
802	MET	N	29.622	11.855	17.813	16.81
803	MET	CA	30.873	11.423	18.408	15.42
804	MET	C	31.414	12.466	19.451	21.03
805	MET	O	31.916	12.180	20.552	17.41
806	MET	CB	31.905	11.171	17.275	15.36
807	MET	CG	33.296	10.921	17.815	15.60
808	MET	SD	34.527	10.644	16.486	19.45
809	MET	CE	34.636	12.330	15.779	16.29
810	VAL	N	31.345	13.741	19.059	17.81
811	VAL	CA	31.809	14.761	19.961	15.34
812	VAL	C	31.027	14.648	21.239	20.80
813	VAL	O	31.512	14.740	22.361	21.08
814	VAL	CB	31.555	16.117	19.308	18.34
815	VAL	CG1	31.720	17.289	20.311	17.11
816	VAL	CG2	32.560	16.297	18.112	16.59
817	TRP	N	29.760	14.465	21.061	23.24
818	TRP	CA	28.891	14.345	22.223	25.45
819	TRP	C	29.223	13.143	23.061	25.99
820	TRP	O	29.403	13.249	24.269	25.20

821	TRP	CB	27.412	14.241	21.777	27.30
822	TRP	CG	26.523	14.219	22.984	30.45
823	TRP	CD1	26.111	13.118	23.651	33.52
824	TRP	CD2	25.979	15.340	23.673	31.02
825	TRP	NE1	25.370	13.477	24.740	33.46
826	TRP	CE2	25.283	14.838	24.787	36.13
827	TRP	CE3	26.031	16.723	23.459	35.07
828	TRP	CZ2	24.642	15.693	25.691	36.39
829	TRP	CZ3	25.390	17.583	24.335	37.49
830	TRP	CH2	24.716	17.061	25.452	38.40
831	GLU	N	29.254	11.979	22.430	20.77
832	GLU	CA	29.484	10.733	23.165	19.32
833	GLU	C	30.849	10.628	23.808	24.59
834	GLU	O	30.997	10.008	24.836	22.28
835	GLU	CB	29.255	9.492	22.281	20.24
836	GLU	CG	27.769	9.267	21.915	22.70
837	GLU	CD	27.538	8.382	20.721	31.58
838	GLU	OE1	28.422	7.828	20.071	28.77
839	GLU	OE2	26.263	8.280	20.456	22.97
840	GLN	N	31.853	11.228	23.201	19.41
841	GLN	CA	33.216	11.131	23.689	18.18
842	GLN	C	33.531	12.204	24.662	20.10
843	GLN	O	34.595	12.205	25.267	21.48
844	GLN	CB	34.246	11.110	22.532	18.95
845	GLN	CG	33.923	9.996	21.532	19.84
846	GLN	CD	33.991	8.651	22.246	39.40
847	GLN	OE1	34.851	8.438	23.105	28.56
848	GLN	NE2	33.079	7.739	21.948	26.05
849	LYS	N	32.598	13.105	24.794	19.33
850	LYS	CA	32.677	14.184	25.768	18.87
851	LYS	C	33.789	15.161	25.514	22.27
852	LYS	O	34.337	15.793	26.422	19.41
853	LYS	CB	32.735	13.639	27.188	21.88
854	LYS	CG	31.398	13.126	27.651	19.83
855	LYS	CD	31.426	12.036	28.700	45.14
856	LYS	CE	30.008	11.554	29.070	76.91
857	LYS	NZ	29.545	10.345	28.337	96.48
858	SER	N	34.066	15.353	24.244	20.79
859	SER	CA	35.092	16.316	23.892	17.81
860	SER	C	34.624	17.729	24.205	21.92
861	SER	O	33.428	18.054	24.168	21.51
862	SER	CB	35.467	16.186	22.410	19.18
863	SER	OG	35.724	14.822	22.082	17.75
864	ARG	N	35.604	18.554	24.504	17.92
865	ARG	CA	35.383	19.949	24.807	16.44
866	ARG	C	35.798	20.801	23.627	19.96

867	ARG	O	35.360	21.920	23.437	19.40
868	ARG	CB	36.288	20.356	25.943	18.45
869	ARG	CG	35.931	21.718	26.512	32.13
870	ARG	CD	36.767	22.844	26.008	47.45
871	ARG	NE	36.397	24.110	26.645	78.03
872	ARG	CZ	35.147	24.537	26.840	72.70
873	ARG	NH1	34.080	23.841	26.491	57.33
874	ARG	NH2	34.975	25.713	27.412	58.72
875	GLY	N	36.733	20.313	22.843	18.99
876	GLY	CA	37.197	21.150	21.735	17.48
877	GLY	C	37.354	20.376	20.447	20.79
878	GLY	O	37.564	19.146	20.464	17.85
879	VAL	N	37.263	21.126	19.331	16.59
880	VAL	CA	37.432	20.590	17.992	13.96
881	VAL	C	38.479	21.445	17.339	19.19
882	VAL	O	38.287	22.668	17.275	20.97
883	VAL	CB	36.129	20.735	17.192	15.20
884	VAL	CG1	36.421	20.354	15.742	14.08
885	VAL	CG2	35.021	19.821	17.752	15.12
886	VAL	N	39.576	20.856	16.870	13.97
887	VAL	CA	40.603	21.610	16.157	11.79
888	VAL	C	40.457	21.284	14.648	18.77
889	VAL	O	40.570	20.121	14.232	18.28
890	VAL	CB	41.958	21.180	16.675	12.96
891	VAL	CG1	43.076	21.854	15.888	14.53
892	VAL	CG2	42.053	21.591	18.138	13.41
893	MET	N	40.169	22.317	13.833	17.03
894	MET	CA	40.019	22.225	12.360	15.40
895	MET	C	41.205	22.846	11.677	18.09
896	MET	O	41.430	24.034	11.821	19.11
897	MET	CB	38.727	22.916	11.923	14.55
898	MET	CG	38.502	22.833	10.454	15.42
899	MET	SD	36.823	23.344	10.018	19.36
900	MET	CE	36.836	23.095	8.223	17.20
901	LEU	N	41.979	22.048	10.954	10.88
902	LEU	CA	43.193	22.584	10.379	10.33
903	LEU	C	43.143	22.854	8.877	13.92
904	LEU	O	44.145	23.245	8.271	14.65
905	LEU	CB	44.326	21.595	10.679	13.36
906	LEU	CG	44.519	21.273	12.178	16.29
907	LEU	CD1	45.594	20.155	12.274	14.38
908	LEU	CD2	45.006	22.542	12.913	13.63
909	ASN	N	41.968	22.712	8.311	13.55
910	ASN	CA	41.826	22.925	6.905	17.04
911	ASN	C	40.701	23.897	6.601	18.91
912	ASN	O	39.965	24.258	7.509	17.09

913	ASN	CB	41.343	21.584	6.310	18.53
914	ASN	CG	39.949	21.183	6.753	18.64
915	ASN	OD1	38.953	21.213	5.995	19.54
916	ASN	ND2	39.867	20.701	7.964	12.69
917	ARG	N	40.583	24.340	5.325	16.20
918	ARG	CA	39.429	25.199	4.934	18.31
919	ARG	C	38.419	24.316	4.226	23.61
920	ARG	O	38.770	23.219	3.769	20.22
921	ARG	CB	39.765	26.336	3.973	19.06
922	ARG	CG	40.782	27.259	4.610	27.14
923	ARG	CD	40.998	28.568	3.854	35.02
924	ARG	NE	41.400	28.489	2.457	76.50
925	ARG	CZ	42.181	27.557	1.889	100.00
926	ARG	NH1	42.629	26.485	2.605	100.00
927	ARG	NH2	42.425	27.679	0.574	74.39
928	VAL	N	37.162	24.772	4.126	17.39
929	VAL	CA	36.162	23.961	3.451	18.47
930	VAL	C	36.529	23.752	1.972	24.72
931	VAL	O	36.433	22.657	1.424	20.57
932	VAL	CB	34.781	24.569	3.651	20.83
933	VAL	CG1	33.815	24.070	2.560	18.89
934	VAL	CG2	34.319	24.222	5.084	18.54
935	MET	N	37.039	24.816	1.331	21.78
936	MET	CA	37.494	24.680	-0.054	22.02
937	MET	C	39.008	24.831	-0.154	23.31
938	MET	O	39.563	25.775	0.348	21.11
939	MET	CB	36.915	25.735	-0.970	24.02
940	MET	CG	37.613	25.464	-2.292	33.60
941	MET	SD	36.695	26.151	-3.672	42.56
942	MET	CE	35.122	25.238	-3.576	37.18
943	GLU	N	39.697	23.938	-0.824	18.74
944	GLU	CA	41.128	24.062	-0.945	18.84
945	GLU	C	41.474	23.440	-2.263	26.07
946	GLU	O	40.841	22.451	-2.688	29.43
947	GLU	CB	41.877	23.271	0.166	21.64
948	GLU	CG	41.562	23.754	1.595	24.84
949	GLU	CD	42.242	22.902	2.628	27.45
950	GLU	OE1	42.453	21.723	2.501	25.26
951	GLU	OE2	42.525	23.545	3.714	24.68
952	LYS	N	42.458	24.000	-2.901	22.86
953	LYS	CA	42.899	23.487	-4.187	23.50
954	LYS	C	41.742	23.348	-5.204	29.15
955	LYS	O	41.767	22.481	-6.061	30.13
956	LYS	CB	43.790	22.226	-4.009	26.67
957	LYS	CG	45.143	22.628	-3.333	33.73
958	LYS	CD	46.022	21.518	-2.773	52.09

959	LYS	CE	47.424	22.009	-2.422	39.14
960	LYS	NZ	48.324	22.031	-3.581	76.66
961	GLY	N	40.695	24.167	-5.076	23.79
962	GLY	CA	39.609	24.073	-6.010	21.74
963	GLY	C	38.631	23.039	-5.693	24.19
964	GLY	O	37.690	22.826	-6.457	29.23
965	SER	N	38.860	22.368	-4.620	16.90
966	SER	CA	37.939	21.336	-4.250	19.52
967	SER	C	37.336	21.506	-2.901	22.34
968	SER	O	37.870	22.237	-2.070	20.15
969	SER	CB	38.620	20.006	-4.177	25.21
970	SER	OG	38.845	19.720	-5.538	47.69
971	LEU	N	36.239	20.761	-2.693	15.65
972	LEU	CA	35.596	20.819	-1.374	14.31
973	LEU	C	36.183	19.731	-0.502	21.78
974	LEU	O	35.871	18.558	-0.677	26.91
975	LEU	CB	34.104	20.610	-1.481	15.29
976	LEU	CG	33.470	21.756	-2.283	21.97
977	LEU	CD1	31.980	21.527	-2.467	21.98
978	LEU	CD2	33.677	23.043	-1.468	26.21
979	LYS	N	37.037	20.122	0.436	17.45
980	LYS	CA	37.741	19.191	1.299	14.44
981	LYS	C	37.009	18.778	2.566	17.63
982	LYS	O	37.488	17.920	3.313	16.36
983	LYS	CB	39.043	19.830	1.755	14.89
984	LYS	CG	39.990	20.179	0.609	20.49
985	LYS	CD	40.109	19.031	-0.365	21.67
986	LYS	CE	41.374	18.235	-0.210	30.52
987	LYS	NZ	41.699	17.355	-1.379	24.68
988	CYS	N	35.889	19.384	2.848	16.47
989	CYS	CA	35.155	19.078	4.070	16.96
990	CYS	C	33.741	19.677	3.961	19.21
991	CYS	O	33.563	20.642	3.244	18.82
992	CYS	CB	35.948	19.897	5.159	16.39
993	CYS	SG	35.331	19.703	6.887	18.71
994	ALA	N	32.760	19.154	4.700	16.15
995	ALA	CA	31.415	19.714	4.739	14.64
996	ALA	C	31.396	20.957	5.690	19.23
997	ALA	O	32.233	21.145	6.585	17.35
998	ALA	CB	30.467	18.651	5.231	13.19
999	GLN	N	30.461	21.869	5.475	21.44
1000	GLN	CA	30.365	23.045	6.336	24.00
1001	GLN	C	29.591	22.536	7.463	24.84
1002	GLN	O	28.375	22.686	7.394	24.39
1003	GLN	CB	29.530	24.166	5.663	26.72
1004	GLN	CG	29.391	25.440	6.544	22.81

1005	GLN	CD	30.676	25.983	7.104	25.37
1006	GLN	OE1	30.793	26.198	8.315	30.89
1007	GLN	NE2	31.616	26.296	6.240	21.26
1008	TYR	N	30.266	21.838	8.409	17.99
1009	TYR	CA	29.535	21.156	9.487	15.44
1010	TYR	C	29.151	21.957	10.748	22.11
1011	TYR	O	28.643	21.358	11.740	18.91
1012	TYR	CB	30.286	19.866	9.883	16.63
1013	TYR	CG	31.599	20.198	10.522	17.61
1014	TYR	CD1	32.752	20.328	9.749	16.52
1015	TYR	CD2	31.683	20.328	11.910	15.79
1016	TYR	CE1	33.967	20.657	10.340	15.78
1017	TYR	CE2	32.904	20.620	12.511	12.70
1018	TYR	CZ	34.026	20.821	11.722	18.43
1019	TYR	OH	35.226	21.088	12.310	18.28
1020	TRP	N	29.389	23.282	10.739	19.64
1021	TRP	CA	29.017	24.082	11.885	20.07
1022	TRP	C	28.335	25.344	11.398	20.86
1023	TRP	O	28.609	25.785	10.296	18.14
1024	TRP	CB	30.276	24.405	12.737	19.79
1025	TRP	CG	31.146	25.427	12.111	20.56
1026	TRP	CD1	31.114	26.769	12.391	23.88
1027	TRP	CD2	32.177	25.255	11.089	19.89
1028	TRP	NE1	32.061	27.448	11.631	23.47
1029	TRP	CE2	32.720	26.554	10.813	23.19
1030	TRP	CE3	32.680	24.162	10.363	21.33
1031	TRP	CZ2	33.724	26.765	9.888	21.55
1032	TRP	CZ3	33.681	24.396	9.418	21.71
1033	TRP	CH2	34.190	25.681	9.187	22.67
1034	PRO	N	27.472	25.933	12.244	19.83
1035	PRO	CA	26.755	27.155	11.892	19.59
1036	PRO	C	27.657	28.375	11.800	23.09
1037	PRO	O	28.534	28.630	12.627	24.72
1038	PRO	CB	25.736	27.390	13.013	20.41
1039	PRO	CG	26.142	26.514	14.203	24.23
1040	PRO	CD	27.223	25.561	13.671	19.47
1041	GLN	N	27.361	29.188	10.787	20.72
1042	GLN	CA	28.094	30.394	10.583	24.35
1043	GLN	C	27.360	31.604	11.131	30.18
1044	GLN	O	27.958	32.680	11.285	28.65
1045	GLN	CB	28.440	30.572	9.138	25.68
1046	GLN	CG	29.324	29.390	8.712	36.40
1047	GLN	CD	29.769	29.566	7.304	56.84
1048	GLN	OE1	28.981	29.299	6.359	45.16
1049	GLN	NE2	30.999	30.080	7.175	51.88
1050	LYS	N	26.094	31.422	11.446	24.00

1051	LYS	CA	25.374	32.529	12.050	23.16
1052	LYS	C	24.547	32.118	13.199	19.74
1053	LYS	O	23.907	31.078	13.158	22.04
1054	LYS	CB	24.653	33.411	11.123	28.65
1055	LYS	CG	23.416	32.791	10.569	74.23
1056	LYS	CD	23.256	33.389	9.195	100.00
1057	LYS	CE	24.577	33.985	8.716	100.00
1058	LYS	NZ	25.063	33.363	7.463	100.00
1059	GLU	N	24.612	32.988	14.210	19.68
1060	GLU	CA	23.924	32.760	15.437	18.75
1061	GLU	C	22.542	32.373	15.160	22.72
1062	GLU	O	22.083	31.334	15.615	21.78
1063	GLU	CB	23.897	34.027	16.333	20.49
1064	GLU	CG	25.250	34.370	17.051	17.63
1065	GLU	CD	26.224	35.178	16.201	22.34
1066	GLU	OE1	26.156	35.277	14.996	23.40
1067	GLU	OE2	27.088	35.835	16.877	20.11
1068	GLU	N	21.820	33.237	14.433	18.53
1069	GLU	CA	20.418	32.935	14.214	19.99
1070	GLU	C	20.107	31.763	13.281	27.09
1071	GLU	O	18.937	31.405	13.088	23.53
1072	GLU	CB	19.614	34.172	13.817	20.56
1073	GLU	CG	20.050	34.671	12.449	21.72
1074	GLU	CD	21.264	35.493	12.560	32.26
1075	GLU	OE1	22.170	35.239	13.292	30.85
1076	GLU	OE2	21.209	36.560	11.870	46.23
1077	LYS	N	21.136	31.153	12.687	24.09
1078	LYS	CA	20.821	30.032	11.815	25.40
1079	LYS	C	21.462	28.780	12.346	32.06
1080	LYS	O	22.539	28.413	11.875	34.08
1081	LYS	CB	21.378	30.287	10.448	25.92
1082	LYS	CG	20.579	31.355	9.738	53.04
1083	LYS	CD	20.028	30.875	8.415	61.11
1084	LYS	CE	18.577	30.432	8.487	81.13
1085	LYS	NZ	18.161	29.607	7.339	100.00
1086	GLU	N	20.846	28.148	13.337	24.74
1087	GLU	CA	21.437	26.950	13.921	24.02
1088	GLU	C	21.324	25.780	12.983	28.33
1089	GLU	O	20.606	25.824	12.017	25.06
1090	GLU	CB	20.762	26.410	15.183	25.15
1091	GLU	CG	19.726	27.239	15.866	51.90
1092	GLU	CD	18.497	27.376	15.063	40.35
1093	GLU	OE1	17.593	26.572	15.036	36.72
1094	GLU	OE2	18.492	28.538	14.496	33.99
1095	MET	N	21.986	24.679	13.350	24.61
1096	MET	CA	21.950	23.455	12.553	21.48

1097	MET	C	21.326	22.368	13.373	27.14
1098	MET	O	21.641	22.217	14.572	26.22
1099	MET	CB	23.369	22.980	12.072	21.43
1100	MET	CG	23.958	23.895	11.019	22.29
1101	MET	SD	25.666	23.460	10.592	26.20
1102	MET	CE	25.256	22.169	9.435	23.94
1103	ILE	N	20.444	21.594	12.707	27.52
1104	ILE	CA	19.811	20.472	13.387	28.07
1105	ILE	C	20.179	19.186	12.668	32.13
1106	ILE	O	20.079	19.113	11.435	30.18
1107	ILE	CB	18.293	20.602	13.485	32.74
1108	ILE	CG1	17.977	21.495	14.686	32.67
1109	ILE	CG2	17.799	19.197	13.784	32.86
1110	ILE	CD1	16.777	22.374	14.453	40.14
1111	PHE	N	20.657	18.208	13.416	23.83
1112	PHE	CA	21.041	16.959	12.785	23.10
1113	PHE	C	19.998	15.956	13.154	25.20
1114	PHE	O	20.027	15.383	14.223	23.48
1115	PHE	CB	22.477	16.491	13.147	22.44
1116	PHE	CG	23.457	17.603	12.869	21.09
1117	PHE	CD1	23.901	17.863	11.574	21.96
1118	PHE	CD2	23.914	18.415	13.901	20.96
1119	PHE	CE1	24.802	18.889	11.307	19.88
1120	PHE	CE2	24.819	19.449	13.666	21.74
1121	PHE	CZ	25.240	19.692	12.360	18.52
1122	GLU	N	19.041	15.794	12.276	26.50
1123	GLU	CA	17.949	14.903	12.589	27.86
1124	GLU	C	18.330	13.470	12.781	32.08
1125	GLU	O	17.727	12.809	13.608	35.43
1126	GLU	CB	16.877	14.981	11.517	30.62
1127	GLU	CG	16.580	16.453	11.155	62.94
1128	GLU	CD	15.389	16.595	10.252	100.00
1129	GLU	OE1	15.483	16.977	9.084	100.00
1130	GLU	OE2	14.265	16.211	10.846	100.00
1131	ASP	N	19.299	12.959	12.012	25.73
1132	ASP	CA	19.656	11.567	12.181	23.02
1133	ASP	C	20.185	11.281	13.545	28.07
1134	ASP	O	19.956	10.200	14.084	29.11
1135	ASP	CB	20.632	11.086	11.107	25.54
1136	ASP	CG	21.905	11.885	11.021	37.00
1137	ASP	OD1	22.084	12.993	11.515	30.66
1138	ASP	OD2	22.789	11.248	10.330	34.51
1139	THR	N	20.935	12.242	14.102	22.93
1140	THR	CA	21.496	12.004	15.402	20.67
1141	THR	C	20.850	12.755	16.525	23.97
1142	THR	O	21.319	12.650	17.645	24.14

1143	THR	CB	23.011	12.160	15.438	24.59
1144	THR	OG1	23.323	13.466	15.015	22.89
1145	THR	CG2	23.629	11.120	14.521	20.72
1146	ASN	N	19.789	13.480	16.239	25.41
1147	ASN	CA	19.071	14.191	17.312	27.59
1148	ASN	C	19.850	15.245	18.085	29.45
1149	ASN	O	19.714	15.298	19.304	27.48
1150	ASN	CB	18.408	13.208	18.326	36.52
1151	ASN	CG	17.000	13.621	18.723	67.20
1152	ASN	OD1	16.346	14.422	18.030	53.22
1153	ASN	ND2	16.539	13.115	19.867	60.40
1154	LEU	N	20.633	16.084	17.377	24.61
1155	LEU	CA	21.440	17.164	17.988	23.07
1156	LEU	C	21.206	18.521	17.335	26.63
1157	LEU	O	21.001	18.634	16.126	23.32
1158	LEU	CB	22.937	16.857	17.853	21.58
1159	LEU	CG	23.337	15.645	18.637	25.34
1160	LEU	CD1	24.640	15.072	18.051	25.68
1161	LEU	CD2	23.514	16.058	20.088	25.96
1162	LYS	N	21.305	19.557	18.160	23.08
1163	LYS	CA	21.182	20.874	17.655	21.49
1164	LYS	C	22.505	21.524	17.940	22.10
1165	LYS	O	23.066	21.305	18.982	23.53
1166	LYS	CB	20.067	21.662	18.336	21.09
1167	LYS	CG	19.870	23.030	17.657	21.83
1168	LYS	CD	18.540	23.701	18.050	20.42
1169	LYS	CE	18.579	24.236	19.482	27.34
1170	LYS	NZ	17.233	24.626	19.969	28.39
1171	LEU	N	22.992	22.343	17.032	21.33
1172	LEU	CA	24.283	22.965	17.219	21.43
1173	LEU	C	24.163	24.452	16.940	23.20
1174	LEU	O	23.767	24.857	15.847	23.59
1175	LEU	CB	25.209	22.322	16.142	22.80
1176	LEU	CG	26.646	22.855	16.136	23.00
1177	LEU	CD1	27.324	22.527	17.442	20.39
1178	LEU	CD2	27.437	22.271	14.965	24.15
1179	THR	N	24.498	25.276	17.874	20.33
1180	THR	CA	24.330	26.697	17.621	20.96
1181	THR	C	25.596	27.533	17.770	20.29
1182	THR	O	26.356	27.291	18.686	22.10
1183	THR	CB	23.364	27.260	18.679	21.96
1184	THR	OG1	22.155	26.543	18.666	22.75
1185	THR	CG2	23.137	28.739	18.365	21.55
1186	LEU	N	25.777	28.540	16.915	16.73
1187	LEU	CA	26.914	29.399	17.070	17.12
1188	LEU	C	26.594	30.412	18.199	25.18

1189	LEU	O	25.599	31.140	18.144	21.33
1190	LEU	CB	27.158	30.194	15.745	18.33
1191	LEU	CG	28.269	31.272	15.781	22.75
1192	LEU	CD1	29.625	30.638	16.105	25.53
1193	LEU	CD2	28.418	31.874	14.386	20.81
1194	ILE	N	27.430	30.433	19.251	22.62
1195	ILE	CA	27.231	31.325	20.365	18.73
1196	ILE	C	28.105	32.558	20.189	25.51
1197	ILE	O	27.689	33.684	20.405	24.71
1198	ILE	CB	27.524	30.585	21.640	17.81
1199	ILE	CG1	26.543	29.420	21.797	17.68
1200	ILE	CG2	27.447	31.544	22.811	19.05
1201	ILE	CD1	25.088	29.851	21.734	20.62
1202	SER	N	29.319	32.399	19.729	20.59
1203	SER	CA	30.136	33.576	19.528	22.30
1204	SER	C	31.333	33.201	18.738	28.89
1205	SER	O	31.682	32.043	18.682	27.38
1206	SER	CB	30.663	34.191	20.812	28.97
1207	SER	OG	31.304	33.178	21.542	43.41
1208	GLU	N	31.978	34.183	18.172	28.09
1209	GLU	CA	33.164	33.904	17.391	31.06
1210	GLU	C	34.245	34.958	17.494	36.63
1211	GLU	O	33.982	36.166	17.532	39.50
1212	GLU	CB	32.762	33.570	15.962	33.57
1213	GLU	CG	33.016	34.695	14.975	57.41
1214	GLU	CD	32.296	34.494	13.672	87.92
1215	GLU	OE1	32.149	33.405	13.128	58.92
1216	GLU	OE2	31.820	35.627	13.204	100.00
1217	ASP	N	35.473	34.500	17.545	25.81
1218	ASP	CA	36.614	35.390	17.665	25.56
1219	ASP	C	37.560	35.177	16.468	33.25
1220	ASP	O	38.298	34.191	16.394	31.20
1221	ASP	CB	37.249	35.034	19.028	29.04
1222	ASP	CG	38.528	35.708	19.390	43.28
1223	ASP	OD1	38.845	36.806	18.949	44.46
1224	ASP	OD2	39.272	34.945	20.175	48.31
1225	ILE	N	37.495	36.089	15.490	30.26
1226	ILE	CA	38.260	36.014	14.247	30.37
1227	ILE	C	39.612	36.677	14.347	31.11
1228	ILE	O	39.742	37.831	14.692	31.83
1229	ILE	CB	37.472	36.612	13.070	34.71
1230	ILE	CG1	36.091	35.991	12.955	36.33
1231	ILE	CG2	38.216	36.607	11.722	35.66
1232	ILE	CD1	34.977	36.984	13.317	65.27
1233	LYS	N	40.627	35.937	14.049	22.86
1234	LYS	CA	41.961	36.472	14.069	23.68

1235	LYS	C	42.448	36.470	12.610	25.39
1236	LYS	O	41.705	36.091	11.707	25.60
1237	LYS	CB	42.921	35.769	15.050	24.58
1238	LYS	CG	42.498	35.848	16.530	30.43
1239	LYS	CD	42.894	37.206	17.140	56.04
1240	LYS	CE	42.275	37.473	18.509	77.38
1241	LYS	NZ	43.040	38.439	19.321	100.00
1242	THR	N	43.669	36.907	12.395	22.88
1243	THR	CA	44.215	36.986	11.049	23.70
1244	THR	C	44.240	35.654	10.392	30.85
1245	THR	O	43.898	35.565	9.210	34.77
1246	THR	CB	45.696	37.481	10.942	30.00
1247	THR	OG1	46.602	36.842	11.798	35.80
1248	THR	CG2	45.878	38.989	10.992	61.05
1249	TYR	N	44.743	34.649	11.108	21.60
1250	TYR	CA	44.882	33.376	10.456	18.56
1251	TYR	C	44.143	32.244	11.082	25.54
1252	TYR	O	44.324	31.078	10.663	28.06
1253	TYR	CB	46.334	33.048	10.304	18.65
1254	TYR	CG	46.986	32.802	11.597	20.73
1255	TYR	CD1	47.329	33.853	12.463	21.11
1256	TYR	CD2	47.327	31.498	11.937	20.37
1257	TYR	CE1	48.003	33.584	13.661	20.41
1258	TYR	CE2	47.992	31.216	13.130	21.74
1259	TYR	CZ	48.327	32.257	13.994	29.63
1260	TYR	OH	49.006	31.917	15.159	23.15
1261	TYR	N	43.337	32.562	12.101	21.11
1262	TYR	CA	42.551	31.528	12.759	22.22
1263	TYR	C	41.350	32.139	13.375	24.48
1264	TYR	O	41.326	33.342	13.534	23.41
1265	TYR	CB	43.342	30.705	13.792	23.10
1266	TYR	CG	43.742	31.476	15.028	22.92
1267	TYR	CD1	44.930	32.194	15.073	20.83
1268	TYR	CD2	42.959	31.415	16.177	24.45
1269	TYR	CE1	45.287	32.851	16.247	21.19
1270	TYR	CE2	43.297	32.082	17.354	21.53
1271	TYR	CZ	44.483	32.785	17.378	21.56
1272	TYR	OH	44.815	33.471	18.512	22.47
1273	THR	N	40.369	31.311	13.688	20.51
1274	THR	CA	39.136	31.768	14.317	20.65
1275	THR	C	38.791	30.762	15.378	25.40
1276	THR	O	38.905	29.535	15.158	21.46
1277	THR	CB	37.933	31.848	13.303	25.48
1278	THR	OG1	38.230	32.801	12.320	23.97
1279	THR	CG2	36.650	32.293	13.969	17.96
1280	VAL	N	38.318	31.309	16.488	19.73

1281	VAL	CA	37.851	30.530	17.623	17.86
1282	VAL	C	36.371	30.790	17.799	23.43
1283	VAL	O	35.931	31.937	17.908	23.75
1284	VAL	CB	38.557	30.926	18.924	22.90
1285	VAL	CG1	38.176	29.946	20.012	23.85
1286	VAL	CG2	40.057	30.808	18.737	23.85
1287	ARG	N	35.609	29.713	17.805	20.09
1288	ARG	CA	34.172	29.781	17.953	19.44
1289	ARG	C	33.699	29.002	19.174	23.12
1290	ARG	O	34.205	27.901	19.557	20.13
1291	ARG	CB	33.431	29.182	16.745	16.93
1292	ARG	CG	33.792	29.938	15.473	24.10
1293	ARG	CD	33.027	29.483	14.215	26.79
1294	ARG	NE	33.620	30.035	12.964	35.76
1295	ARG	CZ	34.769	29.584	12.421	51.01
1296	ARG	NH1	35.509	28.558	12.930	52.65
1297	ARG	NH2	35.199	30.195	11.337	44.38
1298	GLN	N	32.711	29.625	19.799	16.92
1299	GLN	CA	32.040	28.948	20.858	20.12
1300	GLN	C	30.679	28.456	20.290	23.98
1301	GLN	O	29.851	29.207	19.711	23.75
1302	GLN	CB	31.889	29.796	22.106	23.97
1303	GLN	CG	31.076	29.015	23.134	41.20
1304	GLN	CD	30.559	29.958	24.176	67.03
1305	GLN	OE1	31.089	31.100	24.332	52.88
1306	GLN	NE2	29.502	29.485	24.841	56.56
1307	LEU	N	30.494	27.148	20.356	17.61
1308	LEU	CA	29.310	26.552	19.806	18.88
1309	LEU	C	28.563	25.874	20.920	26.36
1310	LEU	O	29.175	25.420	21.914	29.37
1311	LEU	CB	29.714	25.412	18.853	19.47
1312	LEU	CG	30.632	25.859	17.719	24.78
1313	LEU	CD1	31.236	24.593	17.132	23.14
1314	LEU	CD2	29.825	26.634	16.632	19.35
1315	GLU	N	27.268	25.770	20.753	20.30
1316	GLU	CA	26.490	25.073	21.753	19.19
1317	GLU	C	25.861	23.866	21.128	23.29
1318	GLU	O	25.154	23.934	20.078	25.61
1319	GLU	CB	25.419	25.931	22.471	22.13
1320	GLU	CG	24.553	25.130	23.502	24.76
1321	GLU	CD	23.408	26.017	23.909	45.63
1322	GLU	OE1	23.525	26.834	24.760	51.61
1323	GLU	OE2	22.343	25.925	23.137	62.26
1324	LEU	N	26.125	22.751	21.814	21.06
1325	LEU	CA	25.635	21.497	21.378	22.31
1326	LEU	C	24.546	21.016	22.327	27.67

1327	LEU	O	24.761	20.942	23.522	26.01
1328	LEU	CB	26.852	20.528	21.268	24.03
1329	LEU	CG	26.539	19.163	20.645	23.92
1330	LEU	CD1	26.152	19.220	19.149	20.97
1331	LEU	CD2	27.784	18.312	20.815	23.65
1332	GLU	N	23.403	20.711	21.735	25.02
1333	GLU	CA	22.302	20.214	22.466	26.18
1334	GLU	C	21.791	18.886	21.998	33.77
1335	GLU	O	21.443	18.671	20.844	34.24
1336	GLU	CB	21.070	21.145	22.382	28.09
1337	GLU	CG	19.918	20.621	23.287	31.05
1338	GLU	CD	18.778	21.580	23.311	37.23
1339	GLU	OE1	18.856	22.616	22.768	35.92
1340	GLU	OE2	17.717	21.235	23.997	32.19
1341	ASN	N	21.623	18.021	22.954	34.04
1342	ASN	CA	21.013	16.727	22.728	35.49
1343	ASN	C	19.536	17.002	22.721	35.58
1344	ASN	O	18.959	17.366	23.723	36.35
1345	ASN	CB	21.368	15.757	23.883	44.05
1346	ASN	CG	20.671	14.415	23.812	52.92
1347	ASN	OD1	19.515	14.311	23.355	44.48
1348	ASN	ND2	21.363	13.396	24.335	42.29
1349	LEU	N	18.930	16.882	21.595	29.96
1350	LEU	CA	17.542	17.220	21.535	30.39
1351	LEU	C	16.669	16.255	22.278	44.87
1352	LEU	O	15.455	16.484	22.392	46.33
1353	LEU	CB	17.041	17.273	20.108	28.60
1354	LEU	CG	17.610	18.466	19.424	34.04
1355	LEU	CD1	17.221	18.478	17.959	34.74
1356	LEU	CD2	17.091	19.717	20.120	39.55
1357	THR	N	17.269	15.169	22.738	43.23
1358	THR	CA	16.475	14.185	23.405	45.55
1359	THR	C	16.335	14.567	24.850	50.45
1360	THR	O	15.215	14.792	25.347	50.59
1361	THR	CB	17.157	12.816	23.285	71.99
1362	THR	OG1	17.334	12.446	21.931	84.31
1363	THR	CG2	16.334	11.768	24.000	76.78
1364	THR	N	17.522	14.663	25.474	44.41
1365	THR	CA	17.631	14.986	26.856	42.87
1366	THR	C	17.421	16.444	27.075	48.48
1367	THR	O	16.952	16.882	28.107	52.02
1368	THR	CB	18.984	14.575	27.417	55.05
1369	THR	OG1	20.046	15.266	26.798	63.24
1370	THR	CG2	19.150	13.086	27.255	59.51
1371	GLN	N	17.784	17.191	26.081	41.45
1372	GLN	CA	17.729	18.616	26.132	38.83

1373	GLN	C	18.894	19.129	26.948	39.20
1374	GLN	O	18.978	20.280	27.345	40.16
1375	GLN	CB	16.416	19.191	26.628	41.08
1376	GLN	CG	15.319	19.228	25.576	61.17
1377	GLN	CD	14.099	19.968	26.091	89.86
1378	GLN	OE1	13.915	20.136	27.317	69.61
1379	GLN	NE2	13.273	20.437	25.155	100.00
1380	GLU	N	19.813	18.252	27.212	35.40
1381	GLU	CA	21.012	18.645	27.881	35.65
1382	GLU	C	21.902	19.442	26.872	35.40
1383	GLU	O	21.846	19.311	25.623	30.83
1384	GLU	CB	21.695	17.380	28.399	38.29
1385	GLU	CG	23.069	17.598	29.043	53.86
1386	GLU	CD	23.653	16.237	29.306	86.06
1387	GLU	OE1	22.927	15.190	29.234	47.15
1388	GLU	OE2	24.973	16.313	29.499	61.60
1389	THR	N	22.711	20.331	27.382	30.84
1390	THR	CA	23.466	21.110	26.458	30.66
1391	THR	C	24.932	21.176	26.816	36.12
1392	THR	O	25.281	21.143	28.021	33.20
1393	THR	CB	22.790	22.467	26.411	39.57
1394	THR	OG1	22.486	22.795	25.083	53.77
1395	THR	CG2	23.565	23.531	27.180	23.13
1396	ARG	N	25.775	21.267	25.751	30.39
1397	ARG	CA	27.226	21.319	25.923	29.24
1398	ARG	C	27.878	22.407	25.096	25.15
1399	ARG	O	27.469	22.689	23.981	24.36
1400	ARG	CB	27.876	19.985	25.554	35.10
1401	ARG	CG	27.814	18.914	26.635	47.54
1402	ARG	CD	28.971	17.902	26.645	35.93
1403	ARG	NE	28.439	16.717	27.258	45.02
1404	ARG	CZ	28.503	15.548	26.702	70.35
1405	ARG	NH1	29.148	15.393	25.541	42.87
1406	ARG	NH2	27.922	14.522	27.339	59.02
1407	GLU	N	28.876	23.022	25.717	22.49
1408	GLU	CA	29.661	24.057	25.109	21.66
1409	GLU	C	30.904	23.440	24.481	24.49
1410	GLU	O	31.646	22.763	25.168	21.92
1411	GLU	CB	30.223	25.020	26.131	23.64
1412	GLU	CG	31.072	26.050	25.395	37.97
1413	GLU	CD	31.821	26.929	26.332	70.67
1414	GLU	OE1	31.279	27.585	27.207	100.00
1415	GLU	OE2	33.108	26.854	26.147	87.35
1416	ILE	N	31.145	23.707	23.201	20.06
1417	ILE	CA	32.319	23.179	22.541	19.28
1418	ILE	C	33.071	24.345	21.942	22.12

1419	ILE	O	32.454	25.302	21.437	21.81
1420	ILE	CB	31.898	22.286	21.385	22.39
1421	ILE	CG1	30.838	21.236	21.764	21.96
1422	ILE	CG2	33.122	21.719	20.656	20.30
1423	ILE	CD1	31.341	20.178	22.720	24.63
1424	LEU	N	34.376	24.265	21.944	16.47
1425	LEU	CA	35.137	25.326	21.321	16.94
1426	LEU	C	35.661	24.796	20.041	21.55
1427	LEU	O	36.126	23.648	19.980	20.21
1428	LEU	CB	36.341	25.704	22.198	18.75
1429	LEU	CG	35.902	26.118	23.634	26.04
1430	LEU	CD1	37.112	26.450	24.540	27.16
1431	LEU	CD2	35.041	27.336	23.494	24.28
1432	HIS	N	35.635	25.621	19.021	16.36
1433	HIS	CA	36.118	25.183	17.703	14.50
1434	HIS	C	37.275	26.073	17.333	20.44
1435	HIS	O	37.118	27.293	17.360	20.81
1436	HIS	CB	34.956	25.388	16.717	15.22
1437	HIS	CG	35.150	24.834	15.350	17.70
1438	HIS	ND1	35.394	25.650	14.280	18.12
1439	HIS	CD2	35.045	23.553	14.893	18.74
1440	HIS	CE1	35.513	24.853	13.225	17.96
1441	HIS	NE2	35.316	23.575	13.552	17.01
1442	PHE	N	38.456	25.476	17.039	14.68
1443	PHE	CA	39.642	26.223	16.705	14.36
1444	PHE	C	39.905	25.964	15.252	18.76
1445	PHE	O	40.224	24.844	14.924	19.29
1446	PHE	CB	40.854	25.765	17.540	14.14
1447	PHE	CG	40.543	25.886	19.001	15.56
1448	PHE	CD1	40.812	27.078	19.679	19.52
1449	PHE	CD2	39.966	24.812	19.687	19.04
1450	PHE	CE1	40.493	27.165	21.038	21.39
1451	PHE	CE2	39.691	24.853	21.057	21.60
1452	PHE	CZ	39.956	26.053	21.711	19.12
1453	HIS	N	39.729	26.988	14.398	16.34
1454	HIS	CA	39.850	26.842	12.954	16.68
1455	HIS	C	41.036	27.540	12.393	22.59
1456	HIS	O	41.056	28.776	12.342	20.03
1457	HIS	CB	38.597	27.462	12.336	18.43
1458	HIS	CG	38.504	27.092	10.899	22.05
1459	HIS	ND1	37.487	27.555	10.113	21.32
1460	HIS	CD2	39.322	26.311	10.139	23.08
1461	HIS	CE1	37.665	27.073	8.892	20.85
1462	HIS	NE2	38.738	26.297	8.857	22.16
1463	TYR	N	42.029	26.753	11.977	17.95
1464	TYR	CA	43.277	27.301	11.440	17.43

1465	TYR	C	43.022	27.495	9.978	23.32	
1466	TYR	O	42.787	26.542	9.283	19.33	
1467	TYR	CB	44.414	26.250	11.602		16.22
1468	TYR	CG	45.848	26.801	11.601		19.15
1469	TYR	CD1	46.322	27.564	10.527		21.35
1470	TYR	CD2	46.732	26.525	12.639		19.74
1471	TYR	CE1	47.633	28.058	10.473		20.97
1472	TYR	CE2	48.053	26.987	12.600		20.96
1473	TYR	CZ	48.500	27.758	11.521		24.03
1474	TYR	OH	49.771	28.237	11.483		27.87
1475	THR	N	43.075	28.699	9.495	19.92	
1476	THR	CA	42.722	28.877	8.099	22.16	
1477	THR	C	43.882	29.154	7.134	28.45	
1478	THR	O	43.647	29.392	5.946	29.06	
1479	THR	CB	41.656	30.007	8.008	25.85	
1480	THR	OG1	42.260	31.210	8.473	23.68	
1481	THR	CG2	40.470	29.686	8.925	20.99	
1482	THR	N	45.126	29.138	7.580	21.17	
1483	THR	CA	46.174	29.416	6.619	20.89	
1484	THR	C	47.190	28.284	6.556	28.24	
1485	THR	O	48.385	28.506	6.365	28.74	
1486	THR	CB	46.906	30.686	7.023	27.18	
1487	THR	OG1	47.257	30.490	8.372	25.28	
1488	THR	CG2	46.033	31.944	6.834	22.60	
1489	TRP	N	46.743	27.029	6.778	21.40	
1490	TRP	CA	47.670	25.898	6.710	18.45	
1491	TRP	C	47.214	25.059	5.472	23.97	
1492	TRP	O	46.155	24.444	5.460	19.44	
1493	TRP	CB	47.520	25.065	7.977	15.94	
1494	TRP	CG	48.522	23.957	8.065	15.20	
1495	TRP	CD1	49.281	23.420	7.059	17.12	
1496	TRP	CD2	48.839	23.238	9.266	15.16	
1497	TRP	NE1	50.080	22.423	7.592	16.60	
1498	TRP	CE2	49.810	22.295	8.937	19.35	
1499	TRP	CE3	48.376	23.353	10.604		16.48
1500	TRP	CZ2	50.290	21.421	9.907	20.83	
1501	TRP	CZ3	48.843	22.520	11.569		17.13
1502	TRP	CH2	49.763	21.536	11.205		19.65
1503	PRO	N	47.948	25.153	4.377	20.91	
1504	PRO	CA	47.535	24.503	3.150	19.93	
1505	PRO	C	47.609	22.996	3.191	21.72	
1506	PRO	O	48.534	22.409	3.802	19.55	
1507	PRO	CB	48.501	24.984	2.021	23.28	
1508	PRO	CG	49.570	25.796	2.717	28.22	
1509	PRO	CD	49.234	25.901	4.224	21.68	
1510	ASP	N	46.667	22.415	2.435	20.26	

1511	ASP	CA	46.638	20.993	2.325	17.54
1512	ASP	C	48.007	20.561	1.755	23.68
1513	ASP	O	48.601	21.308	0.939	21.00
1514	ASP	CB	45.449	20.625	1.461	15.69
1515	ASP	CG	45.196	19.140	1.667	19.13
1516	ASP	OD1	45.886	18.423	2.440	20.93
1517	ASP	OD2	44.249	18.644	0.903	18.68
1518	PHE	N	48.544	19.411	2.224	16.97
1519	PHE	CA	49.870	18.965	1.826	20.13
1520	PHE	C	50.957	19.945	2.133	25.12
1521	PHE	O	52.103	19.742	1.643	22.55
1522	PHE	CB	49.924	18.631	0.326	26.08
1523	PHE	CG	49.104	17.401	0.246	35.80
1524	PHE	CD1	49.297	16.474	1.282	48.33
1525	PHE	CD2	48.084	17.211	-0.681	40.42
1526	PHE	CE1	48.566	15.292	1.405	48.19
1527	PHE	CE2	47.393	15.996	-0.632	45.67
1528	PHE	CZ	47.618	15.075	0.407	46.93
1529	GLY	N	50.632	21.004	2.915	20.53
1530	GLY	CA	51.683	21.971	3.227	19.53
1531	GLY	C	52.004	22.104	4.708	21.83
1532	GLY	O	51.696	21.221	5.531	18.25
1533	VAL	N	52.661	23.217	5.033	18.02
1534	VAL	CA	53.016	23.487	6.390	16.83
1535	VAL	C	52.534	24.857	6.791	24.11
1536	VAL	O	52.177	25.662	5.955	24.27
1537	VAL	CB	54.512	23.437	6.545	20.78
1538	VAL	CG1	54.973	22.026	6.244	19.08
1539	VAL	CG2	55.079	24.462	5.559	22.82
1540	PRO	N	52.473	25.117	8.096	21.39
1541	PRO	CA	52.081	26.441	8.616	20.99
1542	PRO	C	53.080	27.518	8.157	26.47
1543	PRO	O	54.203	27.218	7.754	25.08
1544	PRO	CB	52.116	26.310	10.170	21.11
1545	PRO	CG	52.245	24.819	10.510	21.50
1546	PRO	CD	52.674	24.115	9.211	19.66
1547	GLU	N	52.696	28.777	8.213	24.24
1548	GLU	CA	53.593	29.831	7.749	23.61
1549	GLU	C	54.886	29.923	8.532	28.04
1550	GLU	O	55.907	30.309	7.997	26.16
1551	GLU	CB	52.881	31.191	7.690	25.09
1552	GLU	CG	51.548	31.090	6.895	64.56
1553	GLU	CD	50.479	32.181	7.111	100.00
1554	GLU	OE1	49.716	32.227	8.113	79.43
1555	GLU	OE2	50.381	33.007	6.070	91.77
1556	SER	N	54.859	29.633	9.821	22.79

1557	SER	CA	56.080	29.729	10.605	20.38
1558	SER	C	55.893	28.889	11.822	23.57
1559	SER	O	54.788	28.588	12.204	24.21
1560	SER	CB	56.352	31.159	11.079	23.98
1561	SER	OG	55.221	31.636	11.819	21.35
1562	PRO	N	56.970	28.495	12.436	22.91
1563	PRO	CA	56.805	27.775	13.649	23.08
1564	PRO	C	56.050	28.657	14.655	26.93
1565	PRO	O	55.238	28.194	15.396	25.45
1566	PRO	CB	58.230	27.505	14.170	24.65
1567	PRO	CG	59.143	27.550	12.965	28.02
1568	PRO	CD	58.397	28.442	11.979	23.89
1569	ALA	N	56.300	29.973	14.661	23.54
1570	ALA	CA	55.629	30.881	15.613	21.90
1571	ALA	C	54.118	30.891	15.479	20.92
1572	ALA	O	53.348	30.851	16.457	19.69
1573	ALA	CB	56.248	32.309	15.569	21.00
1574	SER	N	53.675	30.917	14.234	20.18
1575	SER	CA	52.201	30.957	14.031	21.57
1576	SER	C	51.539	29.677	14.476	24.10
1577	SER	O	50.457	29.670	15.047	23.15
1578	SER	CB	51.769	31.348	12.606	25.87
1579	SER	OG	52.780	31.001	11.688	40.00
1580	PHE	N	52.229	28.573	14.201	19.09
1581	PHE	CA	51.685	27.283	14.553	15.85
1582	PHE	C	51.650	27.200	16.075	21.97
1583	PHE	O	50.659	26.814	16.684	20.90
1584	PHE	CB	52.611	26.166	13.984	18.25
1585	PHE	CG	52.293	24.814	14.607	18.09
1586	PHE	CD1	51.234	24.063	14.104	16.30
1587	PHE	CD2	53.032	24.327	15.687	19.26
1588	PHE	CE1	50.907	22.860	14.722	18.09
1589	PHE	CE2	52.685	23.149	16.344	23.27
1590	PHE	CZ	51.600	22.423	15.850	21.69
1591	LEU	N	52.774	27.544	16.720	20.33
1592	LEU	CA	52.866	27.418	18.177	19.90
1593	LEU	C	51.888	28.318	18.868	23.96
1594	LEU	O	51.233	27.949	19.866	23.17
1595	LEU	CB	54.290	27.689	18.661	20.12
1596	LEU	CG	55.212	26.537	18.324	22.21
1597	LEU	CD1	56.679	26.965	18.499	22.08
1598	LEU	CD2	54.843	25.331	19.215	23.19
1599	ASN	N	51.778	29.520	18.303	22.18
1600	ASN	CA	50.801	30.490	18.835	21.35
1601	ASN	C	49.403	29.847	18.865	21.98
1602	ASN	O	48.693	29.928	19.870	21.88

1603	ASN	CB	50.785	31.816	18.027	20.82
1604	ASN	CG	49.807	32.839	18.619	24.28
1605	ASN	OD1	49.974	33.256	19.783	21.90
1606	ASN	ND2	48.763	33.220	17.844	19.52
1607	PHE	N	49.044	29.156	17.743	18.21
1608	PHE	CA	47.745	28.501	17.628	14.93
1609	PHE	C	47.666	27.300	18.571	19.31
1610	PHE	O	46.638	27.092	19.233	19.07
1611	PHE	CB	47.530	28.099	16.167	15.26
1612	PHE	CG	46.276	27.312	15.946	19.10
1613	PHE	CD1	45.072	27.942	15.602	22.25
1614	PHE	CD2	46.280	25.910	16.038	14.28
1615	PHE	CE1	43.887	27.210	15.433	20.75
1616	PHE	CE2	45.122	25.167	15.823	12.24
1617	PHE	CZ	43.919	25.815	15.533	13.08
1618	LEU	N	48.750	26.511	18.662	18.17
1619	LEU	CA	48.729	25.368	19.546	17.98
1620	LEU	C	48.499	25.780	21.000	21.46
1621	LEU	O	47.707	25.217	21.756	18.26
1622	LEU	CB	50.052	24.635	19.403	18.33
1623	LEU	CG	50.151	23.515	20.450	21.15
1624	LEU	CD1	51.503	22.791	20.311	23.59
1625	LEU	CD2	48.978	22.520	20.369	15.46
1626	PHE	N	49.225	26.808	21.416	20.08
1627	PHE	CA	49.049	27.353	22.789	21.32
1628	PHE	C	47.628	27.968	23.006	24.42
1629	PHE	O	47.052	27.870	24.091	24.60
1630	PHE	CB	50.175	28.286	23.244	20.93
1631	PHE	CG	51.389	27.451	23.568	25.75
1632	PHE	CD1	51.876	26.502	22.666	24.29
1633	PHE	CD2	52.059	27.590	24.788	33.03
1634	PHE	CE1	52.958	25.669	22.967	25.19
1635	PHE	CE2	53.152	26.773	25.100	36.27
1636	PHE	CZ	53.595	25.799	24.198	30.54
1637	LYS	N	47.012	28.564	21.981	19.37
1638	LYS	CA	45.650	29.029	22.169	19.01
1639	LYS	C	44.755	27.830	22.565	23.16
1640	LYS	O	43.965	27.875	23.510	20.57
1641	LYS	CB	45.064	29.654	20.900	20.68
1642	LYS	CG	44.966	31.167	21.019	54.23
1643	LYS	CD	43.679	31.660	21.671	58.81
1644	LYS	CE	43.329	33.110	21.340	79.60
1645	LYS	NZ	42.204	33.258	20.403	90.92
1646	VAL	N	44.903	26.725	21.833	18.90
1647	VAL	CA	44.143	25.527	22.117	17.53
1648	VAL	C	44.447	25.027	23.508	21.15

1649	VAL	O	43.558	24.712	24.284	19.52
1650	VAL	CB	44.432	24.450	21.047	17.34
1651	VAL	CG1	43.692	23.154	21.348	16.63
1652	VAL	CG2	44.052	24.997	19.628	15.16
1653	ARG	N	45.712	24.939	23.832	20.55
1654	ARG	CA	46.047	24.444	25.161	19.47
1655	ARG	C	45.455	25.327	26.259	21.39
1656	ARG	O	44.954	24.911	27.288	21.16
1657	ARG	CB	47.560	24.512	25.353	17.77
1658	ARG	CG	48.312	23.372	24.672	24.26
1659	ARG	CD	49.824	23.590	24.620	22.42
1660	ARG	NE	50.439	22.292	24.419	26.10
1661	ARG	CZ	51.464	21.787	25.113	40.08
1662	ARG	NH1	52.063	22.472	26.095	23.77
1663	ARG	NH2	51.909	20.558	24.796	21.91
1664	GLU	N	45.604	26.581	26.047	20.31
1665	GLU	CA	45.141	27.497	27.028	21.25
1666	GLU	C	43.668	27.493	27.214	26.86
1667	GLU	O	43.228	27.801	28.314	30.19
1668	GLU	CB	45.646	28.874	26.753	23.38
1669	GLU	CG	47.087	28.893	27.173	37.92
1670	GLU	CD	47.736	30.184	26.883	65.18
1671	GLU	OE1	47.282	30.979	26.063	63.04
1672	GLU	OE2	48.853	30.321	27.578	59.99
1673	SER	N	42.897	27.123	26.213	20.78
1674	SER	CA	41.438	27.087	26.408	20.46
1675	SER	C	41.009	26.041	27.387	30.52
1676	SER	O	39.864	25.951	27.744	37.57
1677	SER	CB	40.714	26.707	25.130	17.75
1678	SER	OG	40.998	25.358	24.799	21.13
1679	GLY	N	41.850	25.128	27.755	27.53
1680	GLY	CA	41.324	24.128	28.636	24.97
1681	GLY	C	40.817	22.896	27.894	35.66
1682	GLY	O	40.571	21.813	28.504	38.98
1683	SER	N	40.733	23.002	26.556	26.31
1684	SER	CA	40.241	21.873	25.787	23.11
1685	SER	C	41.002	20.591	25.925	33.29
1686	SER	O	40.402	19.563	25.614	33.64
1687	SER	CB	40.151	22.177	24.303	24.92
1688	SER	OG	39.263	23.274	24.065	24.93
1689	LEU	N	42.318	20.630	26.294	30.38
1690	LEU	CA	43.103	19.378	26.359	30.40
1691	LEU	C	43.108	18.701	27.742	38.35
1692	LEU	O	43.678	17.631	27.992	38.03
1693	LEU	CB	44.513	19.515	25.757	29.26
1694	LEU	CG	44.530	20.316	24.461	31.07

1695	LEU	CD1	45.948	20.591	24.014	27.31
1696	LEU	CD2	43.820	19.572	23.354	34.10
1697	SER	N	42.463	19.367	28.644	34.73
1698	SER	CA	42.363	18.870	29.968	34.22
1699	SER	C	41.847	17.426	30.022	36.01
1700	SER	O	40.925	17.051	29.369	31.19
1701	SER	CB	41.501	19.801	30.780	39.43
1702	SER	OG	41.658	19.437	32.131	55.74
1703	PRO	N	42.456	16.621	30.848	39.48
1704	PRO	CA	42.093	15.228	31.048	39.86
1705	PRO	C	40.730	15.105	31.735	38.86
1706	PRO	O	40.123	14.050	31.847	37.15
1707	PRO	CB	43.162	14.696	31.998	42.88
1708	PRO	CG	43.756	15.909	32.728	48.04
1709	PRO	CD	43.253	17.145	31.996	43.33
1710	GLU	N	40.212	16.194	32.214	32.75
1711	GLU	CA	38.901	16.068	32.791	33.48
1712	GLU	C	37.828	16.086	31.693	31.63
1713	GLU	O	36.656	16.014	31.931	31.89
1714	GLU	CB	38.647	17.159	33.840	37.32
1715	GLU	CG	38.309	18.559	33.240	65.45
1716	GLU	CD	39.318	19.626	33.589	92.79
1717	GLU	OE1	40.366	19.358	34.151	100.00
1718	GLU	OE2	39.027	20.832	33.145	79.45
1719	HIS	N	38.217	16.238	30.459	23.47
1720	HIS	CA	37.246	16.264	29.407	21.41
1721	HIS	C	37.579	15.102	28.544	24.76
1722	HIS	O	38.664	14.584	28.727	24.90
1723	HIS	CB	37.581	17.439	28.476	23.84
1724	HIS	CG	37.356	18.755	29.102	29.53
1725	HIS	ND1	36.121	19.085	29.633	32.52
1726	HIS	CD2	38.191	19.824	29.252	34.49
1727	HIS	CE1	36.203	20.348	30.081	33.65
1728	HIS	NE2	37.441	20.813	29.875	35.22
1729	GLY	N	36.738	14.774	27.539	20.61
1730	GLY	CA	37.086	13.704	26.621	18.66
1731	GLY	C	38.225	14.238	25.771	24.63
1732	GLY	O	38.659	15.427	25.902	26.39
1733	PRO	N	38.720	13.391	24.886	20.23
1734	PRO	CA	39.824	13.749	23.973	16.08
1735	PRO	C	39.406	14.853	23.015	16.63
1736	PRO	O	38.315	14.885	22.519	21.70
1737	PRO	CB	40.065	12.516	23.099	18.85
1738	PRO	CG	39.214	11.419	23.667	23.51
1739	PRO	CD	38.245	12.018	24.690	21.40
1740	VAL	N	40.277	15.758	22.729	17.27

1741	VAL	CA	39.952	16.799	21.788	16.61
1742	VAL	C	39.821	16.100	20.459	20.32
1743	VAL	O	40.473	15.057	20.168	20.45
1744	VAL	CB	41.125	17.820	21.737	20.35
1745	VAL	CG1	42.315	17.135	21.117	22.42
1746	VAL	CG2	40.889	19.002	20.793	20.42
1747	VAL	N	38.972	16.637	19.619	16.18
1748	VAL	CA	38.847	16.060	18.263	13.46
1749	VAL	C	39.700	16.901	17.328	20.85
1750	VAL	O	39.635	18.187	17.316	22.85
1751	VAL	CB	37.396	16.152	17.783	16.77
1752	VAL	CG1	37.337	15.760	16.317	16.82
1753	VAL	CG2	36.566	15.164	18.549	16.12
1754	VAL	N	40.549	16.250	16.565	16.13
1755	VAL	CA	41.389	17.029	15.642	14.73
1756	VAL	C	41.154	16.603	14.236	19.68
1757	VAL	O	41.111	15.408	13.968	18.53
1758	VAL	CB	42.844	16.737	15.897	16.28
1759	VAL	CG1	43.703	17.511	14.901	17.56
1760	VAL	CG2	43.184	17.097	17.349	17.81
1761	HIS	N	40.996	17.532	13.289	15.11
1762	HIS	CA	40.798	17.040	11.911	12.07
1763	HIS	C	41.283	18.025	10.893	18.30
1764	HIS	O	41.478	19.204	11.185	18.91
1765	HIS	CB	39.337	16.682	11.545	13.93
1766	HIS	CG	38.478	17.919	11.267	15.77
1767	HIS	ND1	38.367	18.469	9.979	15.86
1768	HIS	CD2	37.681	18.652	12.088	16.69
1769	HIS	CE1	37.560	19.518	10.045	16.85
1770	HIS	NE2	37.137	19.670	11.291	18.34
1771	CYS	N	41.470	17.478	9.681	16.12
1772	CYS	CA	41.899	18.201	8.547	13.36
1773	CYS	C	40.993	17.660	7.461	17.96
1774	CYS	O	39.874	17.322	7.714	14.94
1775	CYS	CB	43.356	18.020	8.128	12.46
1776	CYS	SG	44.095	16.346	8.360	18.95
1777	SER	N	41.479	17.548	6.218	15.33
1778	SER	CA	40.606	16.949	5.208	15.04
1779	SER	C	40.523	15.407	5.439	18.57
1780	SER	O	39.439	14.799	5.469	17.07
1781	SER	CB	41.042	17.237	3.766	14.15
1782	SER	OG	40.022	16.672	2.921	17.05
1783	ALA	N	41.695	14.781	5.624	14.98
1784	ALA	CA	41.676	13.317	5.798	13.26
1785	ALA	C	41.900	12.903	7.242	18.49
1786	ALA	O	41.702	11.727	7.613	17.47

1787	ALA	CB	42.793	12.703	4.988	14.41
1788	GLY	N	42.343	13.867	8.075	16.70
1789	GLY	CA	42.600	13.538	9.471	15.45
1790	GLY	C	43.930	12.809	9.660	18.39
1791	GLY	O	44.071	11.993	10.600	16.53
1792	ILE	N	44.929	13.082	8.789	13.74
1793	ILE	CA	46.226	12.446	8.919	11.49
1794	ILE	C	47.402	13.347	8.720	18.18
1795	ILE	O	48.386	13.343	9.475	19.37
1796	ILE	CB	46.405	11.141	8.141	16.27
1797	ILE	CG1	46.367	11.366	6.605	17.55
1798	ILE	CG2	45.308	10.153	8.566	15.49
1799	ILE	CD1	46.493	10.057	5.781	14.58
1800	GLY	N	47.379	14.148	7.683	16.11
1801	GLY	CA	48.606	14.939	7.449	16.70
1802	GLY	C	48.766	16.139	8.371	19.48
1803	GLY	O	49.669	16.167	9.200	20.37
1804	ARG	N	47.898	17.159	8.203	14.27
1805	ARG	CA	47.981	18.302	9.086	14.68
1806	ARG	C	47.634	17.835	10.502	17.73
1807	ARG	O	48.295	18.218	11.470	19.43
1808	ARG	CB	47.114	19.444	8.599	12.68
1809	ARG	CG	47.672	20.033	7.287	13.57
1810	ARG	CD	46.645	20.986	6.671	11.34
1811	ARG	NE	45.594	20.244	5.930	16.97
1812	ARG	CZ	44.676	20.854	5.129	31.69
1813	ARG	NH1	44.618	22.185	4.971	16.84
1814	ARG	NH2	43.766	20.109	4.490	15.94
1815	SER	N	46.626	16.986	10.647	15.68
1816	SER	CA	46.298	16.517	12.015	14.86
1817	SER	C	47.460	15.831	12.671	17.12
1818	SER	O	47.726	16.037	13.863	16.53
1819	SER	CB	45.169	15.510	11.989	17.35
1820	SER	OG	44.028	16.136	11.424	17.53
1821	GLY	N	48.157	14.979	11.913	15.45
1822	GLY	CA	49.301	14.268	12.486	11.73
1823	GLY	C	50.394	15.213	12.935	17.63
1824	GLY	O	51.056	15.041	13.964	17.72
1825	THR	N	50.627	16.231	12.100	16.30
1826	THR	CA	51.651	17.225	12.377	15.64
1827	THR	C	51.360	17.997	13.664	19.70
1828	THR	O	52.171	18.184	14.543	17.95
1829	THR	CB	51.794	18.168	11.171	23.66
1830	THR	OG1	52.110	17.428	9.987	19.58
1831	THR	CG2	52.870	19.217	11.433	19.33
1832	PHE	N	50.158	18.420	13.807	15.63

1833	PHE	CA	49.780	19.140	14.983	15.63
1834	PHE	C	49.909	18.259	16.248	20.88
1835	PHE	O	50.425	18.670	17.305	20.45
1836	PHE	CB	48.260	19.563	14.772	17.22
1837	PHE	CG	47.593	20.201	15.997	17.55
1838	PHE	CD1	47.575	21.585	16.155	17.33
1839	PHE	CD2	46.967	19.435	16.983	17.40
1840	PHE	CE1	46.983	22.172	17.278	17.10
1841	PHE	CE2	46.361	20.001	18.114	18.42
1842	PHE	CZ	46.365	21.392	18.257	14.40
1843	CYS	N	49.390	17.033	16.193	17.18
1844	CYS	CA	49.432	16.201	17.366	14.77
1845	CYS	C	50.843	15.806	17.694	21.33
1846	CYS	O	51.225	15.694	18.842	20.61
1847	CYS	CB	48.573	14.933	17.191	18.22
1848	CYS	SG	46.804	15.307	17.081	23.37
1849	LEU	N	51.643	15.520	16.693	19.44
1850	LEU	CA	52.998	15.101	17.015	18.15
1851	LEU	C	53.714	16.200	17.797	19.49
1852	LEU	O	54.425	15.954	18.786	19.58
1853	LEU	CB	53.792	14.823	15.705	16.40
1854	LEU	CG	55.288	14.537	15.965	18.63
1855	LEU	CD1	55.482	13.249	16.751	16.35
1856	LEU	CD2	55.942	14.240	14.617	19.47
1857	ALA	N	53.571	17.449	17.313	16.69
1858	ALA	CA	54.249	18.534	18.012	15.40
1859	ALA	C	53.697	18.630	19.431	19.18
1860	ALA	O	54.419	18.775	20.406	16.89
1861	ALA	CB	54.115	19.859	17.273	14.90
1862	ASP	N	52.390	18.527	19.557	19.72
1863	ASP	CA	51.781	18.658	20.893	17.54
1864	ASP	C	52.338	17.650	21.887	20.70
1865	ASP	O	52.697	17.949	23.038	19.79
1866	ASP	CB	50.237	18.552	20.829	15.42
1867	ASP	CG	49.674	18.953	22.159	24.54
1868	ASP	OD1	50.072	19.914	22.820	19.87
1869	ASP	OD2	48.833	18.076	22.624	22.29
1870	THR	N	52.385	16.427	21.396	16.78
1871	THR	CA	52.782	15.309	22.210	14.97
1872	THR	C	54.217	15.416	22.614	18.91
1873	THR	O	54.563	15.159	23.809	16.57
1874	THR	CB	52.438	13.929	21.591	19.52
1875	THR	OG1	51.035	13.752	21.566	22.01
1876	THR	CG2	53.027	12.780	22.446	15.17
1877	CYS	N	55.074	15.710	21.605	16.93
1878	CYS	CA	56.498	15.818	21.947	16.87

1879	CYS	C	56.751	16.927	22.968	20.74
1880	CYS	O	57.647	16.825	23.812	19.23
1881	CYS	CB	57.335	16.123	20.706	18.21
1882	CYS	SG	57.376	14.721	19.578	21.43
1883	LEU	N	55.983	17.999	22.886	17.24
1884	LEU	CA	56.208	19.110	23.805	16.36
1885	LEU	C	55.758	18.707	25.185	22.13
1886	LEU	O	56.343	19.082	26.201	21.35
1887	LEU	CB	55.501	20.411	23.335	15.49
1888	LEU	CG	56.258	21.020	22.155	16.90
1889	LEU	CD1	55.474	22.152	21.560	18.67
1890	LEU	CD2	57.642	21.489	22.581	19.42
1891	LEU	N	54.709	17.914	25.244	18.58
1892	LEU	CA	54.187	17.454	26.563	19.33
1893	LEU	C	55.127	16.424	27.211	20.57
1894	LEU	O	55.403	16.398	28.406	17.16
1895	LEU	CB	52.758	16.888	26.411	20.29
1896	LEU	CG	52.083	16.494	27.720	23.78
1897	LEU	CD1	51.799	17.757	28.557	22.08
1898	LEU	CD2	50.756	15.824	27.386	26.13
1899	LEU	N	55.661	15.528	26.417	20.05
1900	LEU	CA	56.607	14.567	27.014	22.38
1901	LEU	C	57.798	15.295	27.539	21.44
1902	LEU	O	58.333	14.922	28.548	18.07
1903	LEU	CB	57.204	13.588	25.971	23.67
1904	LEU	CG	56.223	12.489	25.668	30.34
1905	LEU	CD1	56.535	11.952	24.272	35.67
1906	LEU	CD2	56.358	11.418	26.732	23.09
1907	MET	N	58.247	16.315	26.802	17.46
1908	MET	CA	59.411	17.026	27.246	21.88
1909	MET	C	59.093	17.791	28.540	23.63
1910	MET	O	59.925	17.939	29.443	21.17
1911	MET	CB	60.016	17.837	26.046	26.35
1912	MET	CG	60.123	19.321	26.201	31.09
1913	MET	SD	61.319	20.100	25.086	31.12
1914	MET	CE	61.218	18.941	23.667	24.10
1915	ASP	N	57.837	18.250	28.614	21.37
1916	ASP	CA	57.357	18.992	29.777	19.58
1917	ASP	C	57.355	18.111	31.012	26.30
1918	ASP	O	57.669	18.490	32.147	25.46
1919	ASP	CB	55.936	19.493	29.486	18.02
1920	ASP	CG	55.662	20.778	30.190	23.00
1921	ASP	OD1	56.518	21.337	30.864	26.14
1922	ASP	OD2	54.428	21.203	30.067	21.46
1923	LYS	N	56.941	16.910	30.809	26.75
1924	LYS	CA	56.835	15.971	31.911	27.98

1925	LYS	C	58.142	15.701	32.588	30.57
1926	LYS	O	58.233	15.653	33.824	29.41
1927	LYS	CB	56.113	14.673	31.511	31.11
1928	LYS	CG	56.050	13.703	32.679	62.81
1929	LYS	CD	54.796	12.831	32.771	87.49
1930	LYS	CE	54.830	11.905	34.006	100.00
1931	LYS	NZ	54.107	10.613	33.862	100.00
1932	ARG	N	59.175	15.573	31.790	29.07
1933	ARG	CA	60.454	15.266	32.352	31.74
1934	ARG	C	61.458	16.356	32.286	38.39
1935	ARG	O	62.576	16.155	32.699	42.73
1936	ARG	CB	61.007	14.104	31.574	42.79
1937	ARG	CG	60.626	14.244	30.128	44.98
1938	ARG	CD	61.065	13.064	29.267	65.93
1939	ARG	NE	60.195	11.933	29.445	74.57
1940	ARG	CZ	59.885	10.983	28.560	88.88
1941	ARG	NH1	60.356	10.889	27.280	42.03
1942	ARG	NH2	59.037	10.075	29.022	91.14
1943	LYS	N	61.090	17.490	31.753	28.22
1944	LYS	CA	62.065	18.538	31.662	25.40
1945	LYS	C	63.354	18.059	31.041	28.13
1946	LYS	O	64.435	18.477	31.438	25.94
1947	LYS	CB	62.253	19.262	32.958	26.58
1948	LYS	CG	60.936	19.905	33.457	27.81
1949	LYS	CD	60.409	21.051	32.575	14.64
1950	LYS	CE	59.256	21.768	33.219	19.71
1951	LYS	NZ	58.583	22.690	32.312	24.14
1952	ASP	N	63.240	17.207	30.024	22.76
1953	ASP	CA	64.428	16.721	29.406	22.09
1954	ASP	C	64.228	16.564	27.898	30.50
1955	ASP	O	63.820	15.533	27.405	33.52
1956	ASP	CB	64.769	15.377	30.068	24.25
1957	ASP	CG	65.984	14.741	29.416	34.47
1958	ASP	OD1	66.675	15.328	28.608	33.87
1959	ASP	OD2	66.182	13.489	29.778	42.04
1960	PRO	N	64.523	17.584	27.151	24.81
1961	PRO	CA	64.355	17.595	25.725	25.70
1962	PRO	C	65.131	16.551	24.997	31.12
1963	PRO	O	64.707	16.018	23.971	31.92
1964	PRO	CB	64.832	18.944	25.251	29.74
1965	PRO	CG	64.947	19.803	26.511	32.73
1966	PRO	CD	65.066	18.845	27.678	26.52
1967	SER	N	66.264	16.244	25.538	29.07
1968	SER	CA	67.077	15.273	24.890	31.78
1969	SER	C	66.479	13.911	24.933	37.92
1970	SER	O	66.793	13.023	24.150	45.55

1971	SER	CB	68.530	15.309	25.381	42.27
1972	SER	OG	69.183	16.449	24.808	59.55
1973	SER	N	65.580	13.735	25.830	28.18
1974	SER	CA	64.970	12.446	25.947	28.28
1975	SER	C	63.888	12.202	24.886	32.74
1976	SER	O	63.293	11.107	24.796	34.35
1977	SER	CB	64.304	12.317	27.328	30.87
1978	SER	OG	63.068	13.050	27.357	38.21
1979	VAL	N	63.544	13.269	24.191	26.20
1980	VAL	CA	62.453	13.223	23.204	23.76
1981	VAL	C	62.902	12.743	21.809	26.52
1982	VAL	O	63.645	13.435	21.074	28.45
1983	VAL	CB	61.667	14.568	23.186	25.58
1984	VAL	CG1	60.555	14.594	22.126	25.16
1985	VAL	CG2	61.053	14.793	24.553	24.66
1986	ASP	N	62.404	11.567	21.409	21.57
1987	ASP	CA	62.732	11.009	20.111	19.61
1988	ASP	C	61.521	11.154	19.182	26.16
1989	ASP	O	60.569	10.318	19.178	26.94
1990	ASP	CB	63.073	9.533	20.320	22.22
1991	ASP	CG	63.559	8.879	19.072	34.42
1992	ASP	OD1	63.392	9.325	17.935	28.99
1993	ASP	OD2	64.139	7.760	19.353	40.03
1994	ILE	N	61.550	12.245	18.381	23.48
1995	ILE	CA	60.414	12.608	17.503	19.92
1996	ILE	C	59.899	11.503	16.616	24.71
1997	ILE	O	58.701	11.191	16.558	22.68
1998	ILE	CB	60.775	13.880	16.762	20.09
1999	ILE	CG1	60.992	14.906	17.875	22.40
2000	ILE	CG2	59.660	14.316	15.820	17.07
2001	ILE	CD1	61.365	16.303	17.382	33.15
2002	LYS	N	60.844	10.882	15.909	20.78
2003	LYS	CA	60.402	9.864	14.960	21.92
2004	LYS	C	59.744	8.711	15.639	21.66
2005	LYS	O	58.801	8.086	15.176	24.06
2006	LYS	CB	61.517	9.349	14.047	22.87
2007	LYS	CG	62.275	10.451	13.370	20.42
2008	LYS	CD	63.483	9.834	12.671	33.57
2009	LYS	CE	64.772	10.122	13.443	43.45
2010	LYS	NZ	65.169	9.089	14.399	74.10
2011	LYS	N	60.328	8.382	16.736	19.22
2012	LYS	CA	59.802	7.275	17.481	21.33
2013	LYS	C	58.418	7.643	18.006	22.92
2014	LYS	O	57.563	6.767	18.082	18.47
2015	LYS	CB	60.804	6.907	18.595	26.85
2016	LYS	CG	60.510	5.641	19.360	57.18

2017	LYS	CD	61.693	5.220	20.236	74.44
2018	LYS	CE	61.283	4.289	21.393	100.00
2019	LYS	NZ	61.528	4.824	22.754	100.00
2020	VAL	N	58.209	8.943	18.386	20.32
2021	VAL	CA	56.880	9.344	18.869	19.06
2022	VAL	C	55.878	9.249	17.713	19.98
2023	VAL	O	54.733	8.767	17.821	19.01
2024	VAL	CB	56.868	10.755	19.474	21.25
2025	VAL	CG1	55.427	11.187	19.850	18.14
2026	VAL	CG2	57.734	10.742	20.750	21.39
2027	LEU	N	56.348	9.643	16.566	15.76
2028	LEU	CA	55.460	9.554	15.431	15.06
2029	LEU	C	55.086	8.101	15.149	21.46
2030	LEU	O	53.940	7.742	14.839	18.74
2031	LEU	CB	56.111	10.260	14.217	14.15
2032	LEU	CG	55.289	10.130	12.916	18.24
2033	LEU	CD1	53.915	10.764	13.092	16.76
2034	LEU	CD2	56.004	10.808	11.711	17.04
2035	LEU	N	56.064	7.209	15.275	20.58
2036	LEU	CA	55.762	5.798	15.021	18.54
2037	LEU	C	54.783	5.290	16.042	21.57
2038	LEU	O	53.935	4.472	15.713	22.28
2039	LEU	CB	57.015	4.889	14.955	19.53
2040	LEU	CG	57.819	5.029	13.630	24.40
2041	LEU	CD1	59.230	4.498	13.813	22.15
2042	LEU	CD2	57.127	4.319	12.437	21.17
2043	ASP	N	54.883	5.775	17.297	17.91
2044	ASP	CA	53.905	5.330	18.301	16.81
2045	ASP	C	52.538	5.845	17.897	19.40
2046	ASP	O	51.528	5.181	17.996	21.08
2047	ASP	CB	54.203	5.840	19.767	19.29
2048	ASP	CG	53.470	5.056	20.894	46.92
2049	ASP	OD1	53.626	3.832	21.196	39.76
2050	ASP	OD2	52.681	5.849	21.576	67.80
2051	MET	N	52.465	7.082	17.466	17.80
2052	MET	CA	51.146	7.550	17.093	18.08
2053	MET	C	50.586	6.785	15.902	19.16
2054	MET	O	49.360	6.544	15.802	19.67
2055	MET	CB	51.294	9.000	16.640	23.05
2056	MET	CG	51.750	9.946	17.756	33.10
2057	MET	SD	51.452	11.712	17.338	37.23
2058	MET	CE	50.717	12.236	18.903	32.15
2059	ARG	N	51.471	6.425	14.953	16.98
2060	ARG	CA	50.996	5.690	13.759	18.78
2061	ARG	C	50.448	4.309	14.082	20.60
2062	ARG	O	49.921	3.625	13.227	18.40

2063	ARG	CB	51.817	5.867	12.441	25.17
2064	ARG	CG	52.747	7.091	12.429	48.25
2065	ARG	CD	52.842	8.056	11.215	60.15
2066	ARG	NE	52.920	7.361	9.965	30.10
2067	ARG	CZ	53.076	7.701	8.652	25.89
2068	ARG	NH1	53.321	8.890	8.086	27.29
2069	ARG	NH2	53.031	6.649	7.819	19.72
2070	LYS	N	50.600	3.877	15.366	17.55
2071	LYS	CA	50.018	2.617	15.750	16.12
2072	LYS	C	48.516	2.808	15.804	23.50
2073	LYS	O	47.753	1.864	15.744	21.94
2074	LYS	CB	50.439	2.157	17.165	14.21
2075	LYS	CG	51.927	1.901	17.250	18.36
2076	LYS	CD	52.363	1.502	18.666	21.09
2077	LYS	CE	53.863	1.184	18.762	28.07
2078	LYS	NZ	54.278	1.049	20.179	30.77
2079	PHE	N	48.066	4.046	15.996	17.28
2080	PHE	CA	46.649	4.276	16.181	17.04
2081	PHE	C	45.896	4.765	14.955	19.33
2082	PHE	O	44.665	4.622	14.894	17.66
2083	PHE	CB	46.469	5.282	17.315	17.60
2084	PHE	CG	47.096	4.756	18.576	17.54
2085	PHE	CD1	46.372	3.897	19.407	19.62
2086	PHE	CD2	48.368	5.176	18.950	18.66
2087	PHE	CE1	46.943	3.369	20.570	21.35
2088	PHE	CE2	48.910	4.698	20.145	22.41
2089	PHE	CZ	48.214	3.787	20.946	19.04
2090	ARG	N	46.598	5.382	14.053	13.88
2091	ARG	CA	45.967	5.775	12.828	13.48
2092	ARG	C	47.051	5.809	11.774	16.22
2093	ARG	O	48.163	6.250	11.973	15.25
2094	ARG	CB	45.321	7.172	12.939	16.93
2095	ARG	CG	44.544	7.632	11.689	16.86
2096	ARG	CD	43.697	8.897	12.048	18.74
2097	ARG	NE	42.861	9.407	10.923	16.22
2098	ARG	CZ	41.658	8.932	10.504	27.02
2099	ARG	NH1	41.047	7.860	11.071	15.47
2100	ARG	NH2	41.056	9.547	9.443	17.92
2101	MET	N	46.715	5.395	10.564	18.09
2102	MET	CA	47.684	5.410	9.516	18.05
2103	MET	C	47.968	6.814	8.978	20.84
2104	MET	O	47.145	7.697	9.055	18.35
2105	MET	CB	47.079	4.556	8.343	19.02
2106	MET	CG	45.812	5.199	7.720	21.47
2107	MET	SD	45.180	4.334	6.222	26.31
2108	MET	CE	44.495	2.762	6.841	24.21

2109	GLY	N	49.125	6.961	8.363	15.59
2110	GLY	CA	49.540	8.083	7.529	18.21
2111	GLY	C	49.743	9.433	8.135	21.75
2112	GLY	O	49.791	10.451	7.402	18.48
2113	LEU	N	49.925	9.400	9.463	18.42
2114	LEU	CA	50.072	10.648	10.204	14.70
2115	LEU	C	51.314	11.339	9.720	18.00
2116	LEU	O	52.374	10.727	9.794	19.18
2117	LEU	CB	50.061	10.371	11.712	14.05
2118	LEU	CG	48.786	9.649	12.191	17.72
2119	LEU	CD1	48.869	9.460	13.706	17.55
2120	LEU	CD2	47.507	10.393	11.817	15.18
2121	ILE	N	51.159	12.596	9.295	15.02
2122	ILE	CA	52.219	13.420	8.703	15.09
2123	ILE	C	52.350	12.891	7.295	20.09
2124	ILE	O	52.785	11.728	7.088	16.03
2125	ILE	CB	53.538	13.451	9.423	17.27
2126	ILE	CG1	53.244	14.065	10.772	16.88
2127	ILE	CG2	54.476	14.391	8.650	17.72
2128	ILE	CD1	54.453	14.681	11.446	18.43
2129	GLN	N	51.917	13.710	6.331	18.36
2130	GLN	CA	51.887	13.223	4.941	19.19
2131	GLN	C	53.025	13.540	3.983	22.72
2132	GLN	O	53.040	13.026	2.871	20.09
2133	GLN	CB	50.522	13.582	4.326	19.65
2134	GLN	CG	49.371	12.674	4.858	22.65
2135	GLN	CD	49.367	11.349	4.113	26.84
2136	GLN	OE1	49.184	11.364	2.900	17.52
2137	GLN	NE2	49.600	10.236	4.801	19.94
2138	THR	N	53.911	14.414	4.397	21.73
2139	THR	CA	55.045	14.841	3.612	20.72
2140	THR	C	56.262	15.010	4.495	23.82
2141	THR	O	56.210	15.236	5.721	21.43
2142	THR	CB	54.876	16.140	2.852	21.33
2143	THR	OG1	55.050	17.211	3.777	23.48
2144	THR	CG2	53.520	16.222	2.174	16.62
2145	ALA	N	57.378	14.910	3.844	22.77
2146	ALA	CA	58.601	15.018	4.587	23.01
2147	ALA	C	58.801	16.403	5.105	22.21
2148	ALA	O	59.447	16.639	6.154	24.06
2149	ALA	CB	59.776	14.531	3.763	24.53
2150	ASP	N	58.259	17.354	4.370	20.66
2151	ASP	CA	58.422	18.724	4.858	20.24
2152	ASP	C	57.595	18.934	6.129	23.29
2153	ASP	O	57.899	19.740	7.024	23.21
2154	ASP	CB	58.049	19.778	3.806	23.48

2155	ASP	CG	58.591	21.167	4.207	30.38
2156	ASP	OD1	59.693	21.282	4.763	31.02
2157	ASP	OD2	57.785	22.190	3.885	34.64
2158	GLN	N	56.525	18.194	6.208	18.19
2159	GLN	CA	55.712	18.298	7.413	17.86
2160	GLN	C	56.513	17.759	8.615	23.26
2161	GLN	O	56.369	18.212	9.768	21.57
2162	GLN	CB	54.325	17.569	7.239	17.92
2163	GLN	CG	53.295	18.409	6.448	18.27
2164	GLN	CD	52.071	17.609	6.116	19.07
2165	GLN	OE1	52.036	16.389	6.390	18.84
2166	GLN	NE2	51.071	18.282	5.541	16.62
2167	LEU	N	57.349	16.727	8.369	20.85
2168	LEU	CA	58.148	16.126	9.423	17.29
2169	LEU	C	59.161	17.115	9.838	21.68
2170	LEU	O	59.368	17.386	11.015	21.08
2171	LEU	CB	58.770	14.818	8.982	16.92
2172	LEU	CG	59.679	14.141	10.018	18.94
2173	LEU	CD1	58.866	13.624	11.231	17.31
2174	LEU	CD2	60.409	12.959	9.351	15.70
2175	ARG	N	59.781	17.705	8.820	20.27
2176	ARG	CA	60.792	18.727	9.101	19.02
2177	ARG	C	60.181	19.859	9.932	22.20
2178	ARG	O	60.689	20.361	10.947	21.23
2179	ARG	CB	61.327	19.293	7.792	15.51
2180	ARG	CG	62.568	20.163	8.046	21.78
2181	ARG	CD	63.127	20.785	6.770	27.88
2182	ARG	NE	64.351	21.523	7.038	33.02
2183	ARG	CZ	64.355	22.814	7.227	31.22
2184	ARG	NH1	63.242	23.517	7.186	23.06
2185	ARG	NH2	65.508	23.412	7.478	31.35
2186	PHE	N	59.007	20.291	9.471	20.79
2187	PHE	CA	58.378	21.345	10.214	18.33
2188	PHE	C	58.180	20.945	11.680	23.47
2189	PHE	O	58.375	21.746	12.588	22.26
2190	PHE	CB	57.065	21.789	9.582	16.79
2191	PHE	CG	56.399	22.920	10.381	21.31
2192	PHE	CD1	56.681	24.267	10.126	21.18
2193	PHE	CD2	55.431	22.654	11.355	21.09
2194	PHE	CE1	56.063	25.309	10.814	22.40
2195	PHE	CE2	54.836	23.698	12.074	22.51
2196	PHE	CZ	55.164	25.025	11.833	19.57
2197	SER	N	57.752	19.714	11.884	20.57
2198	SER	CA	57.496	19.183	13.233	19.79
2199	SER	C	58.704	19.438	14.082	22.01
2200	SER	O	58.617	19.894	15.216	21.53

2201	SER	CB	57.252	17.666	13.231	16.35
2202	SER	OG	55.984	17.531	12.733	31.09
2203	TYR	N	59.841	19.086	13.544	20.69
2204	TYR	CA	61.030	19.291	14.365	19.51
2205	TYR	C	61.207	20.766	14.689	21.92
2206	TYR	O	61.557	21.130	15.818	20.31
2207	TYR	CB	62.273	18.913	13.583	19.52
2208	TYR	CG	62.654	17.464	13.682	24.16
2209	TYR	CD1	61.877	16.472	13.074	24.17
2210	TYR	CD2	63.872	17.095	14.281	26.60
2211	TYR	CE1	62.245	15.126	13.119	24.68
2212	TYR	CE2	64.261	15.750	14.311	25.92
2213	TYR	CZ	63.440	14.771	13.749	24.97
2214	TYR	OH	63.827	13.469	13.819	32.37
2215	LEU	N	60.985	21.623	13.670	19.51
2216	LEU	CA	61.150	23.020	13.916	17.52
2217	LEU	C	60.225	23.486	15.031	26.06
2218	LEU	O	60.606	24.304	15.892	25.65
2219	LEU	CB	60.860	23.865	12.721	16.93
2220	LEU	CG	61.898	23.718	11.592	26.47
2221	LEU	CD1	61.535	24.606	10.412	24.45
2222	LEU	CD2	63.302	24.080	12.029	28.00
2223	ALA	N	58.990	23.004	15.018	19.08
2224	ALA	CA	58.051	23.437	16.041	16.99
2225	ALA	C	58.424	22.901	17.408	20.57
2226	ALA	O	58.287	23.551	18.424	19.60
2227	ALA	CB	56.587	23.121	15.708	16.41
2228	VAL	N	58.905	21.698	17.488	17.68
2229	VAL	CA	59.206	21.230	18.835	17.05
2230	VAL	C	60.448	21.893	19.395	23.15
2231	VAL	O	60.592	22.155	20.616	21.24
2232	VAL	CB	59.378	19.694	18.826	20.45
2233	VAL	CG1	59.865	19.096	20.165	18.27
2234	VAL	CG2	58.084	19.006	18.357	19.14
2235	ILE	N	61.405	22.100	18.504	21.22
2236	ILE	CA	62.661	22.702	18.937	20.04
2237	ILE	C	62.420	24.090	19.475	25.88
2238	ILE	O	62.999	24.462	20.493	25.47
2239	ILE	CB	63.639	22.794	17.766	24.05
2240	ILE	CG1	64.232	21.403	17.511	25.87
2241	ILE	CG2	64.736	23.758	18.113	22.69
2242	ILE	CD1	64.839	21.250	16.118	27.49
2243	GLU	N	61.577	24.877	18.781	19.27
2244	GLU	CA	61.260	26.237	19.213	17.92
2245	GLU	C	60.385	26.224	20.480	22.75
2246	GLU	O	60.556	27.020	21.388	20.84

2247	GLU	CB	60.510	26.936	18.054	19.09
2248	GLU	CG	59.998	28.359	18.389	20.36
2249	GLU	CD	61.125	29.327	18.744	29.49
2250	GLU	OE1	62.316	29.183	18.463	23.96
2251	GLU	OE2	60.693	30.344	19.428	26.29
2252	GLY	N	59.423	25.296	20.515	20.31
2253	GLY	CA	58.498	25.189	21.643	18.63
2254	GLY	C	59.259	24.833	22.907	23.95
2255	GLY	O	58.870	25.127	24.072	18.97
2256	ALA	N	60.356	24.110	22.677	23.58
2257	ALA	CA	61.188	23.677	23.804	23.19
2258	ALA	C	61.565	24.862	24.682	23.67
2259	ALA	O	61.732	24.708	25.900	25.14
2260	ALA	CB	62.471	22.961	23.330	23.30
2261	LYS	N	61.747	26.038	24.042	19.35
2262	LYS	CA	62.155	27.232	24.809	19.49
2263	LYS	C	61.196	27.564	25.955	25.32
2264	LYS	O	61.575	27.937	27.090	22.02
2265	LYS	CB	62.225	28.423	23.883	21.56
2266	LYS	CG	63.349	28.249	22.857	24.29
2267	LYS	CD	63.327	29.437	21.907	28.63
2268	LYS	CE	64.359	29.447	20.820	33.79
2269	LYS	NZ	63.978	30.470	19.839	63.50
2270	PHE	N	59.922	27.482	25.608	20.00
2271	PHE	CA	58.858	27.740	26.571	17.26
2272	PHE	C	58.834	26.622	27.598	23.66
2273	PHE	O	58.789	26.847	28.791	23.24
2274	PHE	CB	57.543	27.740	25.772	19.05
2275	PHE	CG	56.407	27.958	26.718	23.90
2276	PHE	CD1	55.800	26.859	27.315	30.06
2277	PHE	CD2	56.014	29.242	27.087	25.49
2278	PHE	CE1	54.788	27.010	28.262	31.06
2279	PHE	CE2	54.982	29.400	28.015	30.43
2280	PHE	CZ	54.380	28.294	28.612	28.57
2281	ILE	N	58.841	25.369	27.139	21.16
2282	ILE	CA	58.815	24.235	28.070	21.71
2283	ILE	C	60.001	24.330	29.014	26.83
2284	ILE	O	59.949	23.959	30.185	28.05
2285	ILE	CB	59.014	22.890	27.335	24.04
2286	ILE	CG1	57.843	22.495	26.446	24.85
2287	ILE	CG2	59.269	21.758	28.309	26.71
2288	ILE	CD1	56.488	23.121	26.760	22.80
2289	MET	N	61.117	24.785	28.524	21.30
2290	MET	CA	62.205	24.825	29.440	23.12
2291	MET	C	62.325	26.098	30.299	28.91
2292	MET	O	63.398	26.410	30.748	31.20

2293	MET	CB	63.520	24.378	28.836	25.89
2294	MET	CG	63.303	23.037	28.171	29.97
2295	MET	SD	63.168	21.686	29.352	29.79
2296	MET	CE	64.744	21.950	30.149	26.41
2297	GLY	N	61.278	26.868	30.528	24.26
2298	GLY	CA	61.489	27.964	31.450	24.71
2299	GLY	C	61.414	29.354	30.933	25.55
2300	GLY	O	61.441	30.290	31.708	24.08
2301	ASP	N	61.338	29.535	29.658	21.90
2302	ASP	CA	61.207	30.919	29.246	22.03
2303	ASP	C	59.786	31.173	28.742	27.04
2304	ASP	O	59.433	31.017	27.567	29.25
2305	ASP	CB	62.264	31.272	28.189	25.34
2306	ASP	CG	62.034	32.645	27.603	36.54
2307	ASP	OD1	61.228	33.466	28.063	40.88
2308	ASP	OD2	62.728	32.823	26.512	33.74
2309	SER	N	58.906	31.542	29.605	24.08
2310	SER	CA	57.570	31.757	29.101	26.04
2311	SER	C	57.474	32.994	28.153	33.52
2312	SER	O	56.550	33.100	27.360	33.01
2313	SER	CB	56.523	31.840	30.246	28.08
2314	SER	OG	56.595	30.689	31.114	27.62
2315	SER	N	58.412	33.948	28.264	28.61
2316	SER	CA	58.379	35.156	27.472	26.34
2317	SER	C	58.298	34.830	25.956	32.58
2318	SER	O	57.816	35.629	25.094	30.04
2319	SER	CB	59.651	35.942	27.768	22.72
2320	SER	OG	60.712	35.599	26.864	34.10
2321	VAL	N	58.812	33.647	25.599	28.26
2322	VAL	CA	58.797	33.246	24.170	28.99
2323	VAL	C	57.356	33.239	23.563	32.46
2324	VAL	O	57.093	33.549	22.403	28.95
2325	VAL	CB	59.628	31.965	23.969	29.56
2326	VAL	CG1	58.841	30.740	24.349	27.83
2327	VAL	CG2	60.017	31.836	22.548	31.39
2328	GLN	N	56.370	32.942	24.425	30.24
2329	GLN	CA	54.974	32.874	24.017	29.27
2330	GLN	C	54.503	34.187	23.477	30.84
2331	GLN	O	53.777	34.236	22.506	27.71
2332	GLN	CB	54.073	32.406	25.207	32.06
2333	GLN	CG	52.561	32.481	24.958	56.39
2334	GLN	CD	51.805	31.561	25.885	51.02
2335	GLN	OE1	52.229	31.337	27.004	34.74
2336	GLN	NE2	50.703	31.010	25.403	62.41
2337	ASP	N	54.895	35.262	24.140	29.32
2338	ASP	CA	54.505	36.602	23.691	30.87

2339	ASP	C	55.136	36.911	22.333	30.01
2340	ASP	O	54.530	37.499	21.433	31.24
2341	ASP	CB	54.906	37.629	24.756	35.79
2342	ASP	CG	54.358	37.219	26.082	65.63
2343	ASP	OD1	53.170	36.998	26.227	71.17
2344	ASP	OD2	55.278	37.034	27.014	80.27
2345	GLN	N	56.374	36.460	22.194	25.78
2346	GLN	CA	57.108	36.574	20.948	26.06
2347	GLN	C	56.384	35.851	19.806	30.03
2348	GLN	O	56.246	36.357	18.715	26.89
2349	GLN	CB	58.455	35.924	21.120	27.67
2350	GLN	CG	59.317	36.611	22.198	44.36
2351	GLN	CD	60.751	36.116	22.147	77.73
2352	GLN	OE1	61.283	35.846	21.053	88.38
2353	GLN	NE2	61.357	35.952	23.326	61.19
2354	TRP	N	55.906	34.644	20.070	26.22
2355	TRP	CA	55.195	33.953	19.048	23.95
2356	TRP	C	53.959	34.709	18.716	27.74
2357	TRP	O	53.590	34.825	17.557	29.34
2358	TRP	CB	54.752	32.529	19.487	22.50
2359	TRP	CG	55.887	31.639	19.847	21.30
2360	TRP	CD1	57.167	31.756	19.417	23.75
2361	TRP	CD2	55.842	30.526	20.763	19.48
2362	TRP	NE1	57.927	30.767	19.994	23.42
2363	TRP	CE2	57.143	30.005	20.849	22.89
2364	TRP	CE3	54.820	29.939	21.517	20.00
2365	TRP	CZ2	57.464	28.895	21.668	20.62
2366	TRP	CZ3	55.119	28.829	22.299	20.58
2367	TRP	CH2	56.418	28.303	22.365	20.81
2368	LYS	N	53.273	35.191	19.732	25.02
2369	LYS	CA	52.051	35.913	19.449	23.72
2370	LYS	C	52.279	37.141	18.512	32.33
2371	LYS	O	51.536	37.430	17.531	28.38
2372	LYS	CB	51.390	36.292	20.731	24.86
2373	LYS	CG	50.049	36.954	20.489	36.15
2374	LYS	CD	49.612	37.791	21.672	56.07
2375	LYS	CE	48.105	37.986	21.748	94.91
2376	LYS	NZ	47.664	38.697	22.968	100.00
2377	GLU	N	53.319	37.895	18.808	32.11
2378	GLU	CA	53.630	39.036	17.969	35.38
2379	GLU	C	54.028	38.602	16.559	36.31
2380	GLU	O	53.557	39.097	15.540	38.26
2381	GLU	CB	54.813	39.855	18.548	39.32
2382	GLU	CG	54.559	40.416	19.974	69.72
2383	GLU	CD	53.542	41.540	19.993	100.00
2384	GLU	OE1	53.826	42.742	19.907	100.00

2385	GLU	OE2	52.311	41.071	20.086	100.00
2386	LEU	N	54.930	37.668	16.477	29.59
2387	LEU	CA	55.371	37.218	15.175	29.45
2388	LEU	C	54.297	36.602	14.316	34.02
2389	LEU	O	54.438	36.402	13.095	34.53
2390	LEU	CB	56.402	36.124	15.389	30.02
2391	LEU	CG	57.673	36.730	15.958	37.18
2392	LEU	CD1	58.611	35.621	16.448	36.22
2393	LEU	CD2	58.332	37.541	14.834	39.33
2394	SER	N	53.238	36.196	14.951	26.99
2395	SER	CA	52.226	35.561	14.179	27.01
2396	SER	C	51.217	36.583	13.608	33.85
2397	SER	O	50.359	36.208	12.843	33.74
2398	SER	CB	51.521	34.632	15.134	28.99
2399	SER	OG	50.444	35.407	15.648	44.35
2400	HIS	N	51.275	37.855	14.034	33.50
2401	HIS	CA	50.355	38.935	13.604	36.33
2402	HIS	C	48.945	38.510	13.663	34.53
2403	HIS	O	48.221	38.641	12.668	29.05
2404	HIS	CB	50.574	39.458	12.177	41.53
2405	HIS	CG	52.003	39.597	11.966	50.56
2406	HIS	ND1	52.683	38.801	11.043	55.72
2407	HIS	CD2	52.889	40.377	12.656	55.69
2408	HIS	CE1	53.978	39.152	11.158	56.62
2409	HIS	NE2	54.131	40.085	12.120	56.78
2410	GLU	N	48.528	38.023	14.795	31.47
2411	GLU	CA	47.172	37.560	14.773	32.57
2412	GLU	C	46.110	38.585	14.659	35.60
2413	GLU	O	44.984	38.253	14.397	35.07
2414	GLU	CB	46.886	36.568	15.881	34.05
2415	GLU	CG	47.343	37.124	17.210	29.10
2416	GLU	CD	46.766	36.272	18.291	44.34
2417	GLU	OE1	46.803	35.044	18.311	28.10
2418	GLU	OE2	46.156	36.987	19.183	42.70
2419	ASP	N	46.433	39.851	14.841	38.45
2420	ASP	CA	45.375	40.870	14.777	78.44
2421	ASP	C	45.114	41.525	13.428	73.26
2422	ASP	O	46.027	41.652	12.620	57.37
2423	ASP	CB	45.440	41.851	15.949	80.14
2424	ASP	CG	45.045	41.139	17.215	99.39
2425	ASP	OD1	43.981	40.514	17.333	100.00
2426	ASP	OD2	45.979	41.210	18.148	100.00
2427	HOH	O	38.401	17.896	24.639	19.06
2428	HOH	O	42.880	-2.994	13.734	22.22
2429	HOH	O	37.909	0.024	10.420	18.06
2430	HOH	O	34.283	3.652	13.551	16.99

2431	HOH	O	31.031	7.792	20.003	21.22
2432	HOH	O	56.762	16.414	35.819	23.22
2433	HOH	O	38.520	4.591	3.340	17.34
2434	HOH	O	38.706	8.875	4.448	19.05
2435	HOH	O	48.541	17.369	4.500	18.16
2436	HOH	O	22.375	24.091	20.022	27.04
2437	HOH	O	50.383	3.090	10.757	19.44
2438	HOH	O	56.581	20.545	34.028	23.47
2439	HOH	O	44.023	22.433	27.502	26.90
2440	HOH	O	23.678	29.248	15.041	26.35
2441	HOH	O	30.955	16.693	24.220	25.48
2442	HOH	O	36.539	-2.273	15.479	27.62
2443	HOH	O	60.199	22.714	6.928	25.25
2444	HOH	O	42.799	15.905	24.284	24.08
2445	HOH	O	58.854	31.126	13.755	28.34
2446	HOH	O	25.489	12.276	9.898	29.35
2447	HOH	O	44.868	21.909	30.537	27.95
2448	HOH	O	19.794	30.078	16.536	27.05
2449	HOH	O	41.421	3.661	14.164	17.35
2450	HOH	O	41.884	2.616	3.383	21.00
2451	HOH	O	34.858	3.969	20.688	28.33
2452	HOH	O	53.734	2.425	13.962	22.10
2453	HOH	O	60.930	9.816	23.103	29.63
2454	HOH	O	42.886	3.496	20.674	24.24
2455	HOH	O	30.810	36.766	18.288	26.91
2456	HOH	O	59.810	32.233	32.172	26.16
2457	HOH	O	57.738	17.405	1.262	32.83
2458	HOH	O	36.660	27.108	5.425	23.54
2459	HOH	O	32.265	17.633	1.767	24.56
2460	HOH	O	66.198	17.107	2.407	38.58
2461	HOH	O	57.752	28.197	31.074	29.94
2462	HOH	O	41.286	15.987	26.904	32.37
2463	HOH	O	36.669	27.749	2.270	31.44
2464	HOH	O	39.624	-4.625	16.505	28.88
2465	HOH	O	45.398	24.023	0.668	27.71
2466	HOH	O	51.673	32.445	21.771	23.43
2467	HOH	O	53.099	24.833	2.471	29.74
2468	HOH	O	54.526	19.450	2.810	28.76
2469	HOH	O	27.105	36.172	19.570	24.82
2470	HOH	O	36.334	30.259	9.265	30.82
2471	HOH	O	56.626	24.387	33.815	30.17
2472	HOH	O	42.738	29.954	24.494	35.73
2473	HOH	O	57.220	13.971	0.977	32.27
2474	HOH	O	65.256	29.469	30.089	39.20
2475	HOH	O	49.786	39.709	16.909	43.80
2476	HOH	O	52.863	6.253	24.788	35.18

2477	HOH	O	35.798	-5.535	5.469	31.13
2478	HOH	O	50.331	22.923	-0.657	36.76
2479	HOH	O	36.765	3.406	1.739	42.22
2480	HOH	O	26.434	4.890	5.483	35.83
2481	HOH	O	34.613	32.955	20.594	43.11
2482	HOH	O	27.837	3.167	1.403	42.94
2483	HOH	O	32.582	9.372	-0.315	36.58
2484	HOH	O	45.800	3.147	2.702	31.42
2485	HOH	O	33.763	0.985	2.765	30.40
2486	HOH	O	29.040	1.300	20.110	50.77
2487	HOH	O	42.199	-4.222	6.234	38.97
2488	HOH	O	21.619	20.058	9.321	40.28
2489	HOH	O	53.500	20.656	27.642	27.42
2490	HOH	O	16.860	27.164	18.394	26.90
2491	HOH	O	43.874	0.861	20.343	25.50
2492	HOH	O	29.683	-0.569	10.390	26.21
2493	HOH	O	28.054	11.908	26.787	41.40
2494	HOH	O	50.466	28.546	28.067	42.56
2495	HOH	O	28.502	21.053	3.156	30.33
2496	HOH	O	63.942	27.419	17.604	28.20
2497	HOH	O	22.109	21.232	30.110	48.48
2498	HOH	O	49.254	32.003	23.342	40.08
2499	HOH	O	24.641	7.692	4.830	53.24
2500	HOH	O	63.797	11.089	16.405	27.62
2501	HOH	O	53.333	9.033	24.881	28.87
2502	HOH	O	37.700	0.242	19.127	49.32
2503	HOH	O	24.665	29.142	9.720	48.36
2504	HOH	O	54.352	-3.114	9.194	44.58
2505	HOH	O	62.631	5.916	11.920	39.76
2506	HOH	O	63.952	28.080	27.641	38.19
2507	HOH	O	65.802	19.783	33.411	38.59
2508	HOH	O	57.255	27.489	7.852	41.05
2509	HOH	O	19.030	25.560	24.767	57.85
2510	HOH	O	64.201	13.583	18.348	29.38
2511	HOH	O	55.852	-0.427	22.999	50.13
2512	HOH	O	36.898	-5.489	16.055	67.33
2513	HOH	O	33.905	27.753	6.095	27.01
2514	HOH	O	27.382	-1.372	13.747	35.80
2515	HOH	O	33.489	-3.895	15.708	41.00
2516	HOH	O	24.559	2.258	7.150	41.23
2517	HOH	O	65.779	15.180	21.392	35.84
2518	HOH	O	65.553	25.125	21.639	47.37
2519	HOH	O	32.513	19.611	26.519	62.17
2520	HOH	O	33.651	17.294	28.933	55.49
2521	HOH	O	41.137	19.611	-7.004	52.94
2522	HOH	O	66.395	21.128	4.224	47.91

2523	HOH	O	23.251	11.180	19.061	48.42
2524	HOH	O	39.259	33.229	22.025	51.45
2525	HOH	O	36.119	32.908	9.928	44.34
2526	HOH	O	53.725	36.111	5.937	100.00
2527	HOH	O	63.179	35.153	24.999	55.42
2528	HOH	O	35.968	6.586	-0.582	43.18
2529	HOH	O	21.346	7.913	13.010	56.07
2530	HOH	O	19.175	28.875	19.382	53.38
2531	HOH	O	22.715	7.898	10.565	50.52
2532	HOH	O	47.395	34.116	21.423	47.24
2533	HOH	O	32.765	7.633	26.983	64.04
2534	HOH	O	54.471	34.005	11.028	47.55
2535	HOH	O	72.465	12.809	15.523	46.13
2536	HOH	O	47.441	6.136	-1.870	46.53
2537	HOH	O	43.416	18.301	-3.456	49.44
2538	HOH	O	65.579	21.420	21.981	50.95
2539	HOH	O	47.751	7.411	2.407	40.84
2540	HOH	O	32.644	8.712	8.756	15.74
2541	HOH	O	33.023	11.570	8.792	15.03
2542	HOH	O	44.089	25.927	7.019	19.82
2543	HOH	O	58.775	26.249	32.830	26.89
2544	HOH	O	51.112	4.543	8.642	20.55
2545	HOH	O	62.946	25.839	15.605	26.99
2546	HOH	O	40.881	-6.288	14.710	22.12
2547	HOH	O	52.351	8.308	5.018	25.66
2548	HOH	O	61.224	24.419	33.190	30.44
2549	HOH	O	28.243	-3.909	4.213	32.48
2550	HOH	O	62.221	27.938	13.810	30.53
2551	HOH	O	39.610	-6.610	12.431	30.17
2552	HOH	O	54.043	16.770	35.701	34.80
2553	HOH	O	15.219	28.439	20.359	31.31
2554	HOH	O	64.424	20.767	35.354	32.43
2555	HOH	O	14.987	23.468	24.936	33.81
2556	HOH	O	21.319	29.054	23.219	34.70
2557	HOH	O	30.027	-1.696	12.465	39.40
2558	HOH	O	25.366	15.033	7.774	33.88
2559	HOH	O	66.346	11.979	1.208	42.20
2560	HOH	O	17.665	23.698	26.769	54.87
2561	HOH	O	51.859	5.861	4.981	38.52
2562	HOH	O	24.749	29.791	25.560	42.21
2563	HOH	O	57.813	3.867	18.815	41.01
2564	HOH	O	63.315	26.715	7.503	46.17
2565	HOH	O	53.229	27.524	4.226	50.52
2566	HOH	O	63.148	7.825	9.883	44.30
2567	HOH	O	26.879	19.362	7.236	22.65
2568	HOH	O	67.878	17.615	34.499	44.34

2569	HOH	O	54.054	30.226	31.561	25.96
2570	HOH	O	54.931	12.873	0.470	42.81
2571	HOH	O	44.558	8.294	-3.296	70.17
2572	HOH	O	26.495	26.387	25.981	49.19
2573	HOH	O	45.561	9.651	27.926	47.40
2574	HOH	O	33.903	-6.440	2.953	64.63
2575	HOH	O	64.772	6.818	21.874	47.22
2576	HOH	O	38.599	3.739	20.598	47.72
2577	HOH	O	40.578	33.268	10.218	43.71
2578	HOH	O	23.004	14.669	9.548	41.06
2579	HOH	O	18.520	21.210	10.100	82.04
2580	HOH	O	54.443	0.368	6.856	46.46
2581	HOH	O	53.301	3.094	5.341	55.82
2582	HOH	O	62.577	30.234	15.315	50.03
2583	HOH	O	58.940	24.723	5.711	51.05
2584	HOH	O	20.726	3.366	15.601	78.38
2585	HOH	O	43.027	13.430	27.118	54.39
2586	HOH	O	62.195	28.464	10.795	46.23
2587	HOH	O	50.510	34.226	10.824	39.07
2588	HOH	O	40.918	-2.815	21.009	65.28
2589	HOH	O	43.587	26.925	-2.428	47.56
2590	HOH	O	13.754	15.204	18.843	53.86
2591	HOH	O	31.164	30.490	3.629	56.80
2592	HOH	O	64.794	14.809	1.227	46.20
2593	HOH	O	65.739	6.902	9.576	42.14
2594	HOH	O	22.779	9.377	7.806	74.52
2595	HOH	O	35.536	1.247	20.572	58.11
2596	HOH	O	48.720	41.298	14.904	65.02
2597	HOH	O	41.886	8.125	26.131	43.72
2598	HOH	O	21.553	25.706	8.779	67.26
2599	HOH	O	47.438	24.713	-1.762	68.04
2600	HOH	O	59.462	2.577	16.912	44.01
2601	HOH	O	34.650	13.050	10.584	15.74
2602	HOH	O	44.151	3.876	10.554	20.85
2603	HOH	O	30.226	8.145	9.680	20.38
2604	HOH	O	50.795	5.197	23.429	23.53
2605	HOH	O	55.241	24.256	1.478	43.03
2606	HOH	O	13.876	26.053	19.951	39.87
2607	HOH	O	37.440	7.794	22.997	34.34
2608	HOH	O	36.776	4.942	22.481	44.54
2609	HOH	O	49.204	6.833	4.042	59.47
2610	HOH	O	46.016	15.869	28.666	53.22
2611	HOH	O	52.597	14.225	35.410	44.55
2612	HOH	O	55.717	8.332	23.770	40.53
2613	HOH	O	35.617	38.541	15.729	45.63
2614	HOH	O	24.347	36.908	13.597	48.19

2615	HOH	O	37.734	23.590	30.260	62.04
2616	HOH	O	59.359	7.814	23.351	51.17
2617	HOH	O	40.870	-8.615	10.301	39.22
2618	HOH	O	55.653	-1.953	5.995	52.57
2619	HOH	O	51.582	1.831	22.838	43.21
2620	HOH	O	23.536	16.687	3.287	66.26
2621	HOH	O	27.390	9.583	26.222	66.80
2622	HOH	O	26.006	26.772	7.979	55.20
2623	HOH	O	48.629	36.281	9.258	53.85
2624	HOH	O	54.312	1.731	24.312	49.12
2625	HOH	O	64.534	7.113	16.407	42.12
2626	HOH	O	43.617	30.982	3.143	48.34
2627	HOH	O	22.572	13.132	27.363	70.18
2628	HOH	O	70.408	21.965	2.674	89.51
2629	HOH	O	63.931	33.405	22.517	55.19
2630	HOH	O	48.600	32.735	29.774	71.55
2631	HOH	O	34.250	14.917	30.699	46.61
2632	HOH	O	43.731	33.337	6.158	93.58
2633	HOH	O	60.489	31.207	10.548	55.19
2634	HOH	O	50.155	2.150	6.615	54.57
2635	HOH	O	25.514	6.559	24.332	75.79
2636	HOH	O	31.745	30.209	9.802	50.27
2637	HOH	O	35.679	10.169	26.838	65.87
2638	HOH	O	13.764	16.372	28.336	78.20
2639	HOH	O	17.554	19.418	30.248	64.92
2640	HOH	O	65.875	16.089	34.874	64.83
2641	HOH	O	68.340	17.620	27.806	60.04
2642	HOH	O	36.275	32.819	22.710	48.84
2643	HOH	O	63.468	8.121	24.078	51.50
2644	HOH	O	39.850	34.128	24.551	67.42
2645	HOH	O	22.019	12.665	7.060	70.82
2646	HOH	O	30.890	-4.164	13.154	65.28
2647	HOH	O	23.362	5.115	3.428	51.03
2648	HOH	O	41.079	12.774	28.276	77.64
2649	HOH	O	32.157	37.768	15.682	60.54
2650	HOH	O	37.346	12.911	33.109	69.06
2651	HOH	O	60.400	-0.560	17.559	60.23
1	95	C1	45.324	12.023	1.856	20.00
2	95	S2	45.841	12.927	3.269	20.00
3	95	C3	44.986	14.367	2.692	20.00
4	95	C4	44.391	14.159	1.498	20.00
5	95	C5	44.709	12.824	0.981	20.00
6	95	N6	44.964	15.620	3.482	20.00
7	95	C7	45.489	15.733	4.720	20.00
8	95	C8	45.238	16.996	5.547	20.00
9	95	O9	44.228	17.659	5.375	20.00

10	95	O10	45.978	17.336	6.420	20.00
11	95	O11	46.159	14.860	5.251	20.00
12	95	C12	43.503	15.119	0.776	20.00
13	95	O13	43.428	15.102	-0.452	20.00
14	95	O14	42.803	15.898	1.358	20.00
15	95	C18	44.232	12.358	-0.368	20.00
16	95	C19	44.430	10.836	-0.521	20.00
17	95	N20	45.675	10.345	0.087	20.00
18	95	C21	45.756	10.616	1.531	20.00

TABLE B

Table of the orthogonal three dimensional coordinates in Ångstroms and B factors (Å^2) for Protein Tyrosine Phosphatase 1B complexed with 7-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (Example 26).

No	Amino acid		X	Y	Z	B
1	GLU	N	39.465	52.977	54.384	50.84
2	GLU	CA	38.798	51.719	54.051	51.38
3	GLU	C	39.109	51.267	52.590	49.72
4	GLU	O	38.944	52.002	51.620	49.04
5	GLU	CB	37.270	51.855	54.252	53.79
6	GLU	CG	36.557	50.495	54.416	57.54
7	GLU	CD	36.972	49.698	55.707	62.60
8	GLU	OE1	36.770	50.216	56.799	64.63
9	GLU	OE2	37.518	48.585	55.616	64.40
10	MET	N	39.495	49.971	52.496	46.10
11	MET	CA	39.753	49.178	51.264	42.61
12	MET	C	38.547	49.091	50.363	40.49
13	MET	O	38.640	48.979	49.159	38.08
14	MET	CB	40.128	47.730	51.640	41.62
15	MET	CG	39.190	47.107	52.716	40.45
16	MET	SD	39.645	45.471	53.299	35.84
17	MET	CE	41.295	45.867	53.958	39.51
18	GLU	N	37.419	49.189	51.051	40.04
19	GLU	CA	36.086	49.198	50.457	41.99
20	GLU	C	35.767	50.510	49.639	41.64
21	GLU	O	35.409	50.486	48.472	42.33
22	GLU	CB	35.156	48.876	51.627	43.82
23	GLU	CG	33.862	48.113	51.292	47.17
24	GLU	CD	33.244	47.563	52.607	49.31
25	GLU	OE1	33.732	47.923	53.672	48.56
26	GLU	OE2	32.301	46.761	52.564	51.19
27	LYS	N	36.000	51.696	50.213	40.99
28	LYS	CA	35.753	52.839	49.308	41.50
29	LYS	C	36.854	52.957	48.192	39.57
30	LYS	O	36.534	53.231	47.054	39.12
31	LYS	CB	35.643	54.142	50.104	45.89
32	LYS	CG	34.578	54.185	51.248	51.71
33	LYS	CD	35.008	55.173	52.386	56.13
34	LYS	CE	34.450	54.867	53.793	59.81
35	LYS	NZ	35.323	55.409	54.876	62.35
36	GLU	N	38.147	52.704	48.526	38.42

37	GLU	CA	39.236	52.572	47.517	37.30
38	GLU	C	38.888	51.620	46.385	34.58
39	GLU	O	39.054	51.964	45.238	33.74
40	GLU	CB	40.601	52.140	48.101	40.63
41	GLU	CG	41.526	51.508	47.019	46.16
42	GLU	CD	43.077	51.484	47.114	49.22
43	GLU	OE1	43.672	50.792	47.941	50.86
44	GLU	OE2	43.723	52.146	46.288	51.79
45	PHE	N	38.395	50.433	46.755	31.46
46	PHE	CA	37.835	49.488	45.799	30.49
47	PHE	C	36.777	50.107	44.857	33.05
48	PHE	O	36.828	49.954	43.648	31.17
49	PHE	CB	37.148	48.330	46.531	26.00
50	PHE	CG	36.682	47.268	45.560	23.39
51	PHE	CD1	37.608	46.321	45.069	24.75
52	PHE	CD2	35.388	47.202	45.084	23.83
53	PHE	CE1	37.277	45.364	44.109	21.69
54	PHE	CE2	35.064	46.263	44.099	23.15
55	PHE	CZ	35.985	45.348	43.603	22.50
56	GLU	N	35.818	50.823	45.452	34.78
57	GLU	CA	34.725	51.349	44.619	36.92
58	GLU	C	35.092	52.587	43.702	34.88
59	GLU	O	34.771	52.673	42.529	34.89
60	GLU	CB	33.592	51.542	45.609	42.69
61	GLU	CG	33.191	50.163	46.129	51.81
62	GLU	CD	32.044	50.199	47.121	58.22
63	GLU	OE1	31.735	51.274	47.661	60.76
64	GLU	OE2	31.467	49.123	47.337	60.88
65	GLN	N	35.875	53.523	44.252	32.17
66	GLN	CA	36.614	54.515	43.493	32.79
67	GLN	C	37.270	53.878	42.281	32.59
68	GLN	O	37.068	54.411	41.198	33.38
69	GLN	CB	37.684	55.103	44.398	38.01
70	GLN	CG	38.460	56.386	44.041	46.72
71	GLN	CD	39.538	56.621	45.198	54.60
72	GLN	OE1	40.705	56.281	45.103	58.48
73	GLN	NE2	39.104	57.129	46.335	57.65
74	ILE	N	37.995	52.752	42.495	30.75
75	ILE	CA	38.784	52.110	41.427	29.79
76	ILE	C	37.944	51.513	40.345	29.61
77	ILE	O	38.222	51.644	39.164	28.92
78	ILE	CB	39.820	51.020	41.780	28.01
79	ILE	CG1	40.944	51.578	42.625	26.65
80	ILE	CG2	40.547	50.559	40.485	24.67
81	ILE	CD1	41.717	50.482	43.321	30.61
82	ASP	N	36.941	50.841	40.826	30.56

83	ASP	CA	36.056	50.131	39.941	34.30
84	ASP	C	35.275	51.174	39.066	36.61
85	ASP	O	35.220	51.032	37.847	37.72
86	ASP	CB	35.183	49.189	40.820	34.23
87	ASP	CG	35.372	47.692	40.610	34.09
88	ASP	OD1	36.406	47.266	40.156	34.45
89	ASP	OD2	34.468	46.917	40.892	35.24
90	LYS	N	34.750	52.271	39.708	38.57
91	LYS	CA	34.018	53.296	38.901	40.78
92	LYS	C	34.892	53.932	37.806	40.89
93	LYS	O	34.499	54.071	36.665	41.19
94	LYS	CB	33.321	54.430	39.687	44.73
95	LYS	CG	34.160	55.716	39.765	49.46
96	LYS	CD	33.790	56.625	40.936	52.61
97	LYS	CE	34.890	57.651	41.277	51.86
98	LYS	NZ	36.251	57.064	41.269	49.92
99	SER	N	36.087	54.345	38.162	39.93
100	SER	CA	36.820	54.789	37.003	41.11
101	SER	C	37.425	53.593	36.217	41.60
102	SER	O	37.968	53.748	35.149	44.13
103	SER	CB	37.986	55.539	37.561	41.13
104	SER	OG	38.877	54.652	38.356	43.06
105	GLY	N	37.399	52.386	36.767	39.95
106	GLY	CA	38.129	51.274	36.127	36.83
107	GLY	C	39.671	51.290	36.223	35.39
108	GLY	O	40.316	50.783	35.320	37.15
109	SER	N	40.279	51.841	37.301	32.66
110	SER	CA	41.780	51.938	37.308	31.67
111	SER	C	42.598	50.665	37.811	29.26
112	SER	O	43.741	50.778	38.218	28.04
113	SER	CB	42.337	53.166	38.097	32.05
114	SER	OG	41.454	54.345	38.032	36.33
115	TRP	N	42.019	49.485	37.773	26.65
116	TRP	CA	42.787	48.357	38.207	21.95
117	TRP	C	44.128	48.196	37.429	21.43
118	TRP	O	45.199	48.050	38.019	21.86
119	TRP	CB	41.882	47.101	38.149	22.70
120	TRP	CG	40.932	47.148	39.318	20.91
121	TRP	CD1	39.592	47.426	39.181	21.20
122	TRP	CD2	41.184	47.089	40.757	21.02
123	TRP	NE1	39.031	47.559	40.408	21.97
124	TRP	CE2	39.970	47.310	41.388	20.57
125	TRP	CE3	42.283	46.789	41.551	18.68
126	TRP	CZ2	39.847	47.294	42.770	20.86
127	TRP	CZ3	42.185	46.754	42.958	16.67
128	TRP	CH2	40.956	46.981	43.559	19.85

129	ALA	N	44.103	48.273	36.096	21.75
130	ALA	CA	45.413	48.072	35.405	21.29
131	ALA	C	46.515	49.117	35.696	19.48
132	ALA	O	47.664	48.776	35.736	17.73
133	ALA	CB	45.192	47.958	33.915	21.57
134	ALA	N	46.103	50.326	35.925	21.34
135	ALA	CA	46.952	51.428	36.319	20.36
136	ALA	C	47.471	51.300	37.816	20.18
137	ALA	O	48.633	51.406	38.160	23.47
138	ALA	CB	45.932	52.549	36.136	21.69
139	ILE	N	46.537	50.973	38.753	20.36
140	ILE	CA	47.001	50.649	40.115	20.21
141	ILE	C	48.074	49.511	40.105	19.21
142	ILE	O	49.155	49.583	40.676	20.20
143	ILE	CB	45.776	50.220	40.970	21.58
144	ILE	CG1	44.697	51.339	41.220	25.33
145	ILE	CG2	46.173	49.573	42.320	23.50
146	ILE	CD1	45.051	52.433	42.267	26.28
147	TYR	N	47.688	48.424	39.421	18.90
148	TYR	CA	48.574	47.264	39.255	16.59
149	TYR	C	49.878	47.625	38.498	19.69
150	TYR	O	50.967	47.421	38.997	21.05
151	TYR	CB	47.748	46.176	38.592	15.48
152	TYR	CG	48.537	44.932	38.537	15.58
153	TYR	CD1	48.907	44.209	39.665	15.71
154	TYR	CD2	48.960	44.470	37.316	17.07
155	TYR	CE1	49.695	43.057	39.598	15.33
156	TYR	CE2	49.775	43.341	37.218	18.24
157	TYR	CZ	50.173	42.628	38.344	17.83
158	TYR	OH	50.982	41.544	38.105	16.43
159	GLN	N	49.759	48.251	37.330	20.71
160	GLN	CA	50.882	48.930	36.627	23.54
161	GLN	C	51.839	49.705	37.616	21.33
162	GLN	O	53.047	49.495	37.568	22.52
163	GLN	CB	50.268	49.816	35.499	29.74
164	GLN	CG	49.671	49.057	34.238	43.77
165	GLN	CD	48.539	49.650	33.267	50.76
166	GLN	OE1	47.671	50.472	33.495	53.37
167	GLN	NE2	48.508	49.076	32.066	51.41
168	ASP	N	51.244	50.451	38.587	22.69
169	ASP	CA	51.903	51.194	39.649	23.75
170	ASP	C	52.715	50.305	40.609	21.78
171	ASP	O	53.932	50.387	40.718	21.26
172	ASP	CB	50.890	52.087	40.353	26.73
173	ASP	CG	50.646	53.429	39.655	31.02
174	ASP	OD1	51.574	53.975	39.025	31.00

175	ASP	OD2	49.544	53.975	39.841	32.48
176	ILE	N	52.020	49.333	41.202	20.63
177	ILE	CA	52.741	48.290	41.962	19.38
178	ILE	C	53.874	47.578	41.116	19.66
179	ILE	O	54.989	47.370	41.576	18.07
180	ILE	CB	51.688	47.279	42.579	19.75
181	ILE	CG1	50.762	48.016	43.509	19.61
182	ILE	CG2	52.236	46.021	43.304	16.65
183	ILE	CD1	49.363	47.437	43.437	21.44
184	ARG	N	53.565	47.169	39.884	19.64
185	ARG	CA	54.567	46.484	39.085	22.20
186	ARG	C	55.816	47.437	39.067	22.74
187	ARG	O	56.932	46.979	39.099	20.20
188	ARG	CB	54.023	46.237	37.637	23.80
189	ARG	CG	53.320	44.918	37.290	29.28
190	ARG	CD	53.204	44.519	35.775	38.17
191	ARG	NE	52.689	43.130	35.686	47.71
192	ARG	CZ	53.098	42.163	34.783	46.22
193	ARG	NH1	53.704	42.464	33.629	51.10
194	ARG	NH2	52.965	40.881	35.132	39.82
195	HIS	N	55.615	48.784	39.064	24.89
196	HIS	CA	56.730	49.740	38.862	28.65
197	HIS	C	57.493	50.276	40.108	27.86
198	HIS	O	58.673	50.654	40.038	29.52
199	HIS	CB	56.179	50.983	38.193	36.09
200	HIS	CG	56.811	51.114	36.834	47.89
201	HIS	ND1	58.149	50.961	36.592	52.16
202	HIS	CD2	56.145	51.425	35.625	50.80
203	HIS	CE1	58.303	51.179	35.262	54.85
204	HIS	NE2	57.113	51.465	34.656	55.16
205	GLU	N	56.716	50.341	41.204	24.60
206	GLU	CA	57.222	50.671	42.538	23.35
207	GLU	C	57.907	49.520	43.236	20.84
208	GLU	O	58.770	49.755	44.059	20.77
209	GLU	CB	56.078	51.097	43.441	25.78
210	GLU	CG	55.482	52.418	43.015	34.71
211	GLU	CD	54.294	52.679	43.916	41.97
212	GLU	OE1	54.457	52.660	45.153	47.08
213	GLU	OE2	53.218	52.905	43.375	42.03
214	ALA	N	57.458	48.299	42.919	20.22
215	ALA	CA	58.071	47.145	43.572	18.85
216	ALA	C	59.618	47.108	43.413	19.60
217	ALA	O	60.137	47.773	42.539	21.31
218	ALA	CB	57.514	45.879	42.928	17.65
219	SER	N	60.263	46.351	44.323	17.44
220	SER	CA	61.700	46.463	44.627	17.65

221	SER	C	62.475	45.590	43.693	20.44
222	SER	O	61.875	44.737	43.028	20.82
223	SER	CB	61.987	45.892	46.086	16.87
224	SER	OG	60.908	46.087	47.088	17.03
225	ASP	N	63.806	45.769	43.757	23.65
226	ASP	CA	64.608	44.993	42.881	25.32
227	ASP	C	65.953	44.653	43.545	24.00
228	ASP	O	66.834	45.495	43.638	25.47
229	ASP	CB	64.577	45.897	41.647	30.03
230	ASP	CG	65.409	45.356	40.505	35.94
231	ASP	OD1	65.782	44.168	40.576	37.82
232	ASP	OD2	65.652	46.122	39.542	40.50
233	PHE	N	66.128	43.392	44.016	20.26
234	PHE	CA	67.429	43.035	44.653	17.74
235	PHE	C	68.199	42.026	43.725	19.63
236	PHE	O	67.571	41.347	42.920	18.88
237	PHE	CB	67.148	42.482	46.088	15.74
238	PHE	CG	66.400	43.443	47.024	14.99
239	PHE	CD1	67.009	44.602	47.475	14.29
240	PHE	CD2	65.081	43.181	47.458	11.07
241	PHE	CE1	66.294	45.491	48.252	13.28
242	PHE	CE2	64.379	44.048	48.267	12.04
243	PHE	CZ	64.998	45.216	48.653	14.86
244	PRO	N	69.545	41.908	43.722	19.03
245	PRO	CA	70.154	40.759	43.057	17.74
246	PRO	C	69.576	39.346	43.319	17.59
247	PRO	O	69.475	38.926	44.441	18.11
248	PRO	CB	71.601	40.765	43.541	17.29
249	PRO	CG	71.547	41.671	44.730	17.67
250	PRO	CD	70.462	42.691	44.470	17.97
251	CYS	N	69.285	38.589	42.224	16.91
252	CYS	CA	69.204	37.088	42.281	16.83
253	CYS	C	70.495	36.319	41.751	17.10
254	CYS	O	70.417	35.519	40.790	15.98
255	CYS	CB	68.007	36.580	41.502	17.42
256	CYS	SG	66.580	37.626	41.691	21.76
257	ARG	N	71.667	36.666	42.348	17.15
258	ARG	CA	72.970	36.242	41.791	19.32
259	ARG	C	73.119	34.699	41.788	19.49
260	ARG	O	73.496	34.047	40.814	19.32
261	ARG	CB	74.079	36.850	42.622	24.18
262	ARG	CG	74.980	37.833	41.912	34.75
263	ARG	CD	75.311	39.152	42.663	42.80
264	ARG	NE	75.471	39.097	44.113	51.13
265	ARG	CZ	74.828	39.887	45.009	51.47
266	ARG	NH1	74.701	41.151	44.646	48.86

267	ARG	NH2	74.350	39.441	46.136	48.27
268	VAL	N	72.830	34.041	42.924	17.97
269	VAL	CA	72.998	32.576	42.948	16.80
270	VAL	C	71.992	31.806	41.998	15.05
271	VAL	O	72.306	30.779	41.377	15.45
272	VAL	CB	73.273	32.034	44.312	18.01
273	VAL	CG1	72.573	30.756	44.520	15.99
274	VAL	CG2	72.876	32.942	45.388	17.07
275	ALA	N	70.819	32.430	41.831	14.53
276	ALA	CA	69.795	31.819	41.038	14.43
277	ALA	C	70.213	31.697	39.659	15.46
278	ALA	O	69.747	30.800	38.995	16.10
279	ALA	CB	68.535	32.680	41.126	12.61
280	LYS	N	71.076	32.655	39.323	17.52
281	LYS	CA	71.665	32.762	37.982	17.70
282	LYS	C	72.998	32.019	37.847	19.60
283	LYS	O	73.580	32.004	36.776	22.60
284	LYS	CB	71.858	34.261	37.582	19.24
285	LYS	CG	70.573	35.200	37.622	19.97
286	LYS	CD	69.498	34.765	36.639	21.69
287	LYS	CE	68.278	35.680	36.497	24.74
288	LYS	NZ	67.268	34.860	35.757	26.46
289	LEU	N	73.581	31.431	38.936	20.39
290	LEU	CA	74.928	30.843	38.665	19.13
291	LEU	C	74.792	29.677	37.700	21.96
292	LEU	O	73.908	28.875	37.880	20.82
293	LEU	CB	75.585	30.242	39.923	18.89
294	LEU	CG	75.924	31.268	40.972	17.87
295	LEU	CD1	76.848	32.313	40.400	19.14
296	LEU	CD2	76.506	30.672	42.266	17.39
297	PRO	N	75.721	29.419	36.742	23.61
298	PRO	CA	75.299	28.411	35.767	24.44
299	PRO	C	75.014	27.017	36.391	22.23
300	PRO	O	74.374	26.171	35.790	23.82
301	PRO	CB	76.375	28.491	34.687	26.16
302	PRO	CG	76.896	29.926	34.822	27.75
303	PRO	CD	76.869	30.196	36.324	26.72
304	LYS	N	75.512	26.800	37.638	22.30
305	LYS	CA	75.166	25.529	38.233	22.26
306	LYS	C	73.654	25.317	38.489	22.91
307	LYS	O	73.187	24.168	38.569	25.95
308	LYS	CB	76.067	25.121	39.358	23.13
309	LYS	CG	75.991	25.832	40.660	24.19
310	LYS	CD	76.895	25.038	41.664	27.45
311	LYS	CE	77.506	25.823	42.852	31.65
312	LYS	NZ	77.983	24.871	43.905	37.10

313	ASN	N	72.908	26.422	38.604	20.49
314	ASN	CA	71.547	26.288	39.034	18.95
315	ASN	C	70.578	26.384	37.886	19.83
316	ASN	O	69.364	26.402	38.110	16.61
317	ASN	CB	71.326	27.301	40.083	15.32
318	ASN	CG	72.319	27.082	41.210	18.08
319	ASN	OD1	72.774	25.998	41.593	16.89
320	ASN	ND2	72.630	28.223	41.762	17.04
321	LYS	N	71.115	26.261	36.653	19.50
322	LYS	CA	70.198	26.533	35.517	20.65
323	LYS	C	68.970	25.582	35.499	17.99
324	LYS	O	67.827	25.897	35.252	17.79
325	LYS	CB	71.102	26.415	34.280	24.77
326	LYS	CG	70.705	27.324	33.113	35.23
327	LYS	CD	71.780	27.296	31.993	43.17
328	LYS	CE	71.506	28.319	30.877	48.79
329	LYS	NZ	72.095	27.908	29.585	51.89
330	ASN	N	69.249	24.336	35.828	16.87
331	ASN	CA	68.139	23.356	35.844	17.37
332	ASN	C	67.428	23.162	37.209	14.52
333	ASN	O	67.042	22.047	37.553	14.87
334	ASN	CB	68.758	22.008	35.522	17.56
335	ASN	CG	69.723	21.326	36.476	21.16
336	ASN	OD1	70.099	21.716	37.568	23.28
337	ASN	ND2	70.132	20.210	35.940	22.37
338	ARG	N	67.435	24.272	37.960	13.45
339	ARG	CA	66.851	24.363	39.265	14.08
340	ARG	C	65.834	25.455	39.226	11.72
341	ARG	O	64.908	25.455	39.985	11.90
342	ARG	CB	67.927	24.635	40.349	14.72
343	ARG	CG	68.808	23.399	40.637	15.03
344	ARG	CD	69.531	23.566	41.958	13.22
345	ARG	NE	70.329	22.382	42.127	14.96
346	ARG	CZ	70.786	22.027	43.336	15.87
347	ARG	NH1	70.387	22.635	44.429	14.76
348	ARG	NH2	71.629	21.021	43.409	16.81
349	ASN	N	65.990	26.376	38.305	12.70
350	ASN	CA	64.823	27.286	38.125	12.44
351	ASN	C	63.866	26.703	37.067	12.58
352	ASN	O	64.316	26.017	36.196	11.79
353	ASN	CB	65.333	28.584	37.553	15.34
354	ASN	CG	66.254	29.036	38.579	15.14
355	ASN	OD1	65.853	29.008	39.721	13.40
356	ASN	ND2	67.478	29.375	38.192	15.01
357	ARG	N	62.602	26.959	37.101	11.31
358	ARG	CA	61.750	26.422	36.097	10.21

359	ARG	C	61.344	27.550	35.032	11.77
360	ARG	O	60.942	27.244	33.909	10.43
361	ARG	CB	60.569	25.882	36.926	10.53
362	ARG	CG	59.435	25.507	35.982	9.14
363	ARG	CD	58.083	25.567	36.545	10.01
364	ARG	NE	57.805	24.437	37.372	10.47
365	ARG	CZ	57.604	23.255	36.784	10.78
366	ARG	NH1	57.345	22.981	35.539	11.53
367	ARG	NH2	57.847	22.305	37.582	10.00
368	TYR	N	61.531	28.839	35.419	12.06
369	TYR	CA	61.406	29.958	34.471	10.98
370	TYR	C	62.644	30.880	34.512	13.59
371	TYR	O	63.313	31.085	35.519	15.53
372	TYR	CB	60.188	30.734	34.879	9.94
373	TYR	CG	58.902	29.947	34.781	11.54
374	TYR	CD1	58.528	29.222	33.627	11.75
375	TYR	CD2	58.104	29.917	35.903	10.70
376	TYR	CE1	57.373	28.429	33.600	12.58
377	TYR	CE2	56.968	29.113	35.885	11.42
378	TYR	CZ	56.577	28.348	34.738	12.61
379	TYR	OH	55.482	27.467	34.686	13.20
380	ARG	N	63.021	31.367	33.315	13.40
381	ARG	CA	64.268	32.148	33.315	16.28
382	ARG	C	63.947	33.436	34.160	14.00
383	ARG	O	64.804	34.093	34.720	16.44
384	ARG	CB	64.600	32.319	31.810	17.48
385	ARG	CG	65.513	33.475	31.434	23.38
386	ARG	CD	65.168	34.185	30.101	28.56
387	ARG	NE	63.860	34.904	30.168	32.94
388	ARG	CZ	63.004	34.975	29.117	34.20
389	ARG	NH1	63.482	34.836	27.908	33.58
390	ARG	NH2	61.715	35.089	29.282	33.15
391	ASP	N	62.671	33.824	34.184	12.94
392	ASP	CA	62.305	35.149	34.663	12.52
393	ASP	C	61.714	35.183	36.027	12.63
394	ASP	O	61.194	36.232	36.433	11.75
395	ASP	CB	61.233	35.719	33.744	13.44
396	ASP	CG	61.768	36.276	32.470	15.48
397	ASP	OD1	62.985	36.503	32.404	14.91
398	ASP	OD2	60.953	36.507	31.556	17.68
399	VAL	N	61.838	34.020	36.724	12.12
400	VAL	CA	61.386	33.871	38.121	11.29
401	VAL	C	62.363	33.150	39.073	9.78
402	VAL	O	62.300	31.998	39.482	11.48
403	VAL	CB	59.862	33.736	38.326	16.11
404	VAL	CG1	59.564	33.071	39.708	15.44

405	VAL	CG2	59.003	33.367	37.026	14.33
406	SER	N	63.292	34.043	39.508	10.16
407	SER	CA	64.351	33.658	40.430	11.16
408	SER	C	64.044	34.235	41.838	9.64
409	SER	O	63.282	35.201	41.980	11.51
410	SER	CB	65.674	34.207	39.868	10.81
411	SER	OG	65.795	34.206	38.393	12.18
412	PRO	N	64.652	33.603	42.890	8.67
413	PRO	CA	64.679	34.069	44.300	10.79
414	PRO	C	65.739	35.174	44.607	13.35
415	PRO	O	66.863	35.054	44.167	14.81
416	PRO	CB	65.070	32.742	45.027	10.00
417	PRO	CG	65.954	31.994	44.070	10.77
418	PRO	CD	65.350	32.343	42.713	9.16
419	PHE	N	65.333	36.312	45.288	13.59
420	PHE	CA	66.396	37.309	45.592	12.71
421	PHE	C	67.463	36.637	46.469	12.31
422	PHE	O	67.099	35.793	47.313	12.68
423	PHE	CB	65.827	38.538	46.324	9.81
424	PHE	CG	64.721	39.284	45.705	10.06
425	PHE	CD1	64.796	39.648	44.360	9.58
426	PHE	CD2	63.667	39.689	46.481	9.41
427	PHE	CE1	63.839	40.478	43.828	10.26
428	PHE	CE2	62.712	40.531	45.935	10.02
429	PHE	CZ	62.810	40.954	44.617	8.64
430	ASP	N	68.731	37.039	46.301	11.62
431	ASP	CA	69.699	36.442	47.229	12.07
432	ASP	C	69.336	36.779	48.740	12.27
433	ASP	O	69.471	35.939	49.614	15.21
434	ASP	CB	71.090	36.960	46.918	13.40
435	ASP	CG	71.585	36.819	45.512	14.25
436	ASP	OD1	71.510	35.755	45.001	15.72
437	ASP	OD2	72.114	37.776	44.954	12.79
438	HIS	N	68.891	37.987	49.110	12.16
439	HIS	CA	68.936	38.332	50.537	12.71
440	HIS	C	68.037	37.415	51.373	13.92
441	HIS	O	68.357	37.023	52.468	15.61
442	HIS	CB	68.619	39.807	50.639	12.05
443	HIS	CG	67.189	40.229	50.532	10.80
444	HIS	ND1	66.218	40.158	51.532	11.89
445	HIS	CD2	66.595	40.810	49.442	10.89
446	HIS	CE1	65.078	40.670	51.055	9.38
447	HIS	NE2	65.292	41.065	49.801	11.30
448	SER	N	66.911	37.032	50.727	13.43
449	SER	CA	65.732	36.268	51.219	12.13
450	SER	C	65.616	34.786	50.742	12.76

451	SER	O	64.852	33.988	51.280	13.37
452	SER	CB	64.459	36.969	50.655	10.16
453	SER	OG	64.073	36.712	49.237	10.34
454	ARG	N	66.289	34.396	49.662	11.78
455	ARG	CA	66.110	33.011	49.184	13.97
456	ARG	C	66.308	32.030	50.330	13.85
457	ARG	O	67.052	32.388	51.228	11.86
458	ARG	CB	67.182	32.758	48.072	12.96
459	ARG	CG	68.663	32.686	48.534	13.81
460	ARG	CD	69.587	31.920	47.602	13.20
461	ARG	NE	70.951	31.816	48.184	14.78
462	ARG	CZ	71.552	30.688	48.524	15.00
463	ARG	NH1	70.936	29.557	48.478	11.82
464	ARG	NH2	72.784	30.639	48.884	17.64
465	ILE	N	65.654	30.828	50.300	14.21
466	ILE	CA	65.948	29.645	51.217	12.58
467	ILE	C	67.155	28.748	50.720	14.61
468	ILE	O	67.216	28.241	49.587	15.26
469	ILE	CB	64.722	28.774	51.313	13.58
470	ILE	CG1	63.510	29.500	51.879	13.29
471	ILE	CG2	64.977	27.447	52.006	13.64
472	ILE	CD1	63.571	29.924	53.338	13.30
473	LYS	N	68.150	28.621	51.612	15.82
474	LYS	CA	69.276	27.764	51.318	15.98
475	LYS	C	69.096	26.360	51.954	17.60
476	LYS	O	68.984	26.265	53.135	19.95
477	LYS	CB	70.448	28.373	52.073	17.28
478	LYS	CG	70.639	29.851	51.912	17.24
479	LYS	CD	72.028	30.137	52.423	22.81
480	LYS	CE	72.374	31.627	52.475	26.05
481	LYS	NZ	73.787	31.719	52.904	31.86
482	LEU	N	69.186	25.284	51.179	17.25
483	LEU	CA	69.191	23.986	51.803	18.29
484	LEU	C	70.420	23.813	52.707	20.34
485	LEU	O	71.463	24.451	52.542	19.70
486	LEU	CB	69.326	23.009	50.654	18.28
487	LEU	CG	68.077	22.606	49.875	18.66
488	LEU	CD1	68.503	22.354	48.425	17.13
489	LEU	CD2	66.905	23.584	50.003	14.98
490	HIS	N	70.327	22.853	53.607	22.86
491	HIS	CA	71.473	22.568	54.469	25.86
492	HIS	C	72.376	21.544	53.818	30.06
493	HIS	O	72.823	20.636	54.478	31.82
494	HIS	CB	71.011	22.101	55.889	26.12
495	HIS	CG	70.169	23.121	56.652	25.12
496	HIS	ND1	69.669	22.796	57.857	25.76

497	HIS	CD2	69.771	24.443	56.370	24.91
498	HIS	CE1	68.999	23.876	58.293	25.52
499	HIS	NE2	69.054	24.883	57.439	26.33
500	GLN	N	72.654	21.694	52.528	32.94
501	GLN	CA	73.476	20.669	51.845	36.50
502	GLN	C	74.845	21.250	51.490	37.97
503	GLN	O	74.997	22.462	51.350	37.18
504	GLN	CB	72.785	19.969	50.653	37.95
505	GLN	CG	72.220	20.893	49.533	40.06
506	GLN	CD	71.786	20.148	48.187	44.06
507	GLN	OE1	72.396	20.225	47.103	46.49
508	GLN	NE2	70.689	19.404	48.371	41.49
509	GLU	N	75.833	20.321	51.371	41.15
510	GLU	CA	77.175	20.785	50.982	41.70
511	GLU	C	77.356	20.946	49.420	39.31
512	GLU	O	78.061	21.828	48.944	38.68
513	GLU	CB	78.182	19.780	51.511	45.57
514	GLU	CG	78.185	19.584	53.033	54.22
515	GLU	CD	78.719	18.188	53.518	60.23
516	GLU	OE1	79.014	17.293	52.706	63.36
517	GLU	OE2	78.813	18.019	54.741	62.48
518	ASP	N	76.708	20.105	48.601	38.53
519	ASP	CA	77.055	20.312	47.192	37.73
520	ASP	C	76.579	21.706	46.692	33.50
521	ASP	O	77.309	22.594	46.250	35.46
522	ASP	CB	76.361	19.144	46.491	43.21
523	ASP	CG	76.711	19.135	45.008	49.96
524	ASP	OD1	77.838	19.533	44.702	53.55
525	ASP	OD2	75.843	18.784	44.184	52.89
526	ASN	N	75.262	21.863	46.853	28.37
527	ASN	CA	74.553	23.027	46.358	21.99
528	ASN	C	73.354	23.441	47.299	20.24
529	ASN	O	72.312	22.805	47.353	21.87
530	ASN	CB	74.099	22.536	44.960	19.04
531	ASN	CG	73.717	23.704	44.039	18.04
532	ASN	OD1	73.456	24.765	44.530	19.25
533	ASN	ND2	73.728	23.588	42.734	15.06
534	ASP	N	73.466	24.546	48.022	18.00
535	ASP	CA	72.332	25.033	48.836	18.78
536	ASP	C	71.151	25.681	48.030	17.35
537	ASP	O	70.225	26.206	48.623	18.81
538	ASP	CB	72.886	26.063	49.861	19.48
539	ASP	CG	73.288	27.453	49.333	23.10
540	ASP	OD1	72.887	27.851	48.256	24.35
541	ASP	OD2	73.983	28.207	50.021	29.58
542	TYR	N	71.212	25.740	46.675	16.55

543	TYR	CA	70.199	26.452	45.895	12.98
544	TYR	C	68.875	25.687	45.783	12.27
545	TYR	O	68.835	24.576	45.292	12.81
546	TYR	CB	70.772	26.662	44.525	10.36
547	TYR	CG	69.834	27.547	43.751	12.42
548	TYR	CD1	69.670	28.900	44.065	10.55
549	TYR	CD2	69.026	27.003	42.736	11.80
550	TYR	CE1	68.666	29.636	43.411	11.79
551	TYR	CE2	68.002	27.711	42.094	10.71
552	TYR	CZ	67.821	29.072	42.453	9.67
553	TYR	OH	66.838	29.931	41.987	10.99
554	ILE	N	67.843	26.362	46.233	13.06
555	ILE	CA	66.470	26.037	45.852	12.41
556	ILE	C	65.728	27.348	45.344	11.32
557	ILE	O	66.023	28.445	45.836	12.19
558	ILE	CB	65.643	25.321	46.943	12.98
559	ILE	CG1	64.216	25.028	46.401	8.76
560	ILE	CG2	65.631	26.109	48.238	10.91
561	ILE	CD1	63.534	23.768	46.941	9.88
562	ASN	N	64.802	27.274	44.373	9.16
563	ASN	CA	63.961	28.432	44.113	9.65
564	ASN	C	62.777	28.477	45.134	10.37
565	ASN	O	61.669	28.001	44.902	10.07
566	ASN	CB	63.409	28.368	42.689	9.08
567	ASN	CG	62.854	29.669	42.094	9.54
568	ASN	OD1	62.064	30.411	42.717	10.96
569	ASN	ND2	63.215	29.836	40.823	9.06
570	ALA	N	63.053	29.245	46.232	9.41
571	ALA	CA	62.074	29.518	47.285	10.05
572	ALA	C	62.490	30.729	48.081	11.58
573	ALA	O	63.684	31.012	48.161	12.92
574	ALA	CB	62.248	28.369	48.268	7.50
575	SER	N	61.501	31.398	48.688	10.51
576	SER	CA	61.767	32.622	49.448	11.23
577	SER	C	60.986	32.733	50.725	10.85
578	SER	O	59.810	32.408	50.715	12.48
579	SER	CB	61.240	33.808	48.570	7.55
580	SER	OG	61.832	33.943	47.206	10.45
581	LEU	N	61.665	33.227	51.759	11.48
582	LEU	CA	61.028	33.484	53.026	12.53
583	LEU	C	60.459	34.863	52.839	13.15
584	LEU	O	61.162	35.810	52.745	13.65
585	LEU	CB	62.100	33.317	54.125	13.18
586	LEU	CG	61.714	33.026	55.617	15.58
587	LEU	CD1	60.346	32.465	56.032	15.45
588	LEU	CD2	61.990	34.242	56.446	15.90

589	ILE	N	59.142	34.963	52.710	12.91
590	ILE	CA	58.433	36.244	52.854	13.87
591	ILE	C	58.199	36.410	54.383	16.47
592	ILE	O	57.520	35.626	55.029	16.73
593	ILE	CB	57.078	36.103	52.126	13.55
594	ILE	CG1	57.058	36.090	50.580	12.82
595	ILE	CG2	56.084	37.173	52.640	16.67
596	ILE	CD1	58.184	35.285	49.937	12.75
597	LYS	N	58.754	37.425	54.954	16.38
598	LYS	CA	58.733	37.584	56.393	19.03
599	LYS	C	57.916	38.848	56.792	18.79
600	LYS	O	58.361	39.997	56.871	18.39
601	LYS	CB	60.193	37.663	56.758	24.89
602	LYS	CG	60.382	37.380	58.215	36.70
603	LYS	CD	61.837	37.012	58.412	45.35
604	LYS	CE	62.107	36.507	59.815	49.89
605	LYS	NZ	63.542	36.156	59.861	53.29
606	MET	N	56.632	38.598	57.069	17.44
607	MET	CA	55.789	39.713	57.508	17.07
608	MET	C	56.013	39.963	59.034	17.04
609	MET	O	55.491	39.236	59.879	16.87
610	MET	CB	54.344	39.363	57.116	15.46
611	MET	CG	54.239	38.984	55.611	15.47
612	MET	SD	55.075	40.191	54.531	16.71
613	MET	CE	53.670	41.304	54.490	12.89
614	GLU	N	56.792	41.029	59.352	20.27
615	GLU	CA	57.059	41.404	60.754	22.54
616	GLU	C	55.827	42.015	61.552	22.33
617	GLU	O	55.304	41.421	62.490	24.08
618	GLU	CB	58.262	42.322	60.762	26.36
619	GLU	CG	58.891	42.457	62.173	35.25
620	GLU	CD	59.916	43.590	62.166	40.00
621	GLU	OE1	59.477	44.700	61.830	43.15
622	GLU	OE2	61.096	43.345	62.480	43.54
623	GLU	N	55.283	43.165	61.103	23.41
624	GLU	CA	54.028	43.623	61.715	24.81
625	GLU	C	52.959	42.499	61.936	24.74
626	GLU	O	52.437	42.295	63.015	24.77
627	GLU	CB	53.482	44.704	60.837	26.99
628	GLU	CG	52.576	45.679	61.608	35.79
629	GLU	CD	51.974	46.718	60.634	45.06
630	GLU	OE1	52.430	46.765	59.511	48.32
631	GLU	OE2	51.091	47.475	61.022	49.68
632	ALA	N	52.665	41.750	60.868	22.17
633	ALA	CA	51.673	40.706	60.947	21.64
634	ALA	C	52.213	39.523	61.660	22.46

635	ALA	O	51.470	38.690	62.105	24.05
636	ALA	CB	51.310	40.191	59.565	20.53
637	GLN	N	53.508	39.446	61.797	23.74
638	GLN	CA	53.951	38.375	62.649	27.80
639	GLN	C	53.494	36.942	62.164	26.92
640	GLN	O	53.212	36.073	62.988	27.71
641	GLN	CB	53.604	38.695	64.142	32.88
642	GLN	CG	54.557	39.626	64.990	40.36
643	GLN	CD	55.637	38.789	65.755	47.19
644	GLN	OE1	55.413	38.194	66.807	52.84
645	GLN	NE2	56.809	38.690	65.144	46.59
646	ARG	N	53.576	36.814	60.781	23.43
647	ARG	CA	53.512	35.548	59.983	18.91
648	ARG	C	54.532	35.508	58.799	16.84
649	ARG	O	54.660	36.485	58.081	17.96
650	ARG	CB	52.108	35.410	59.417	18.58
651	ARG	CG	51.983	33.974	58.874	16.36
652	ARG	CD	50.561	33.599	58.555	17.70
653	ARG	NE	49.917	33.327	59.836	17.29
654	ARG	CZ	48.629	33.215	59.998	15.94
655	ARG	NH1	47.869	33.433	58.973	13.68
656	ARG	NH2	48.184	32.917	61.156	18.40
657	SER	N	55.331	34.440	58.582	13.82
658	SER	CA	56.164	34.277	57.366	12.48
659	SER	C	55.588	33.151	56.471	11.37
660	SER	O	54.899	32.287	56.921	13.16
661	SER	CB	57.601	33.787	57.603	12.86
662	SER	OG	58.317	33.977	58.878	19.01
663	TYR	N	56.004	33.108	55.215	11.99
664	TYR	CA	55.704	31.895	54.458	10.12
665	TYR	C	56.953	31.593	53.701	10.62
666	TYR	O	57.730	32.497	53.459	11.32
667	TYR	CB	54.616	32.184	53.384	10.39
668	TYR	CG	53.469	33.063	53.849	10.08
669	TYR	CD1	53.696	34.400	54.011	10.55
670	TYR	CD2	52.208	32.580	54.154	10.53
671	TYR	CE1	52.769	35.233	54.522	12.90
672	TYR	CE2	51.239	33.420	54.642	12.10
673	TYR	CZ	51.530	34.723	54.834	13.13
674	TYR	OH	50.524	35.465	55.346	13.22
675	ILE	N	57.104	30.369	53.235	10.35
676	ILE	CA	58.077	30.153	52.147	7.97
677	ILE	C	57.178	30.151	50.851	9.78
678	ILE	O	56.263	29.348	50.833	10.25
679	ILE	CB	58.953	28.883	52.458	9.05
680	ILE	CG1	59.740	29.088	53.740	10.20

681	ILE	CG2	59.957	28.496	51.397	8.37
682	ILE	CD1	60.474	27.819	54.246	8.33
683	LEU	N	57.403	31.084	49.833	8.73
684	LEU	CA	56.855	30.922	48.465	8.66
685	LEU	C	57.905	30.236	47.526	11.10
686	LEU	O	59.110	30.576	47.552	12.49
687	LEU	CB	56.561	32.244	47.860	9.65
688	LEU	CG	55.257	32.826	48.326	10.58
689	LEU	CD1	54.913	34.147	47.565	11.19
690	LEU	CD2	55.270	32.940	49.838	12.47
691	THR	N	57.402	29.203	46.761	10.83
692	THR	CA	58.299	28.363	45.895	8.06
693	THR	C	57.668	28.097	44.482	9.10
694	THR	O	56.489	28.380	44.264	8.53
695	THR	CB	58.859	27.100	46.647	8.87
696	THR	OG1	59.976	26.366	45.972	11.27
697	THR	CG2	57.803	26.211	47.344	8.63
698	GLN	N	58.506	27.610	43.519	7.55
699	GLN	CA	57.990	27.172	42.176	7.51
700	GLN	C	57.437	25.750	42.219	8.15
701	GLN	O	57.723	24.997	43.143	9.26
702	GLN	CB	59.060	27.244	41.087	7.72
703	GLN	CG	60.130	26.188	41.317	7.48
704	GLN	CD	61.257	26.336	40.384	7.54
705	GLN	OE1	61.977	25.398	40.166	13.65
706	GLN	NE2	61.511	27.505	39.888	6.16
707	GLY	N	56.603	25.377	41.221	8.70
708	GLY	CA	56.238	23.982	41.272	8.95
709	GLY	C	57.520	23.130	41.108	10.89
710	GLY	O	58.254	23.333	40.156	12.56
711	PRO	N	57.762	22.179	42.005	11.90
712	PRO	CA	58.999	21.445	41.898	10.45
713	PRO	C	59.179	20.901	40.444	12.59
714	PRO	O	58.192	20.592	39.776	12.30
715	PRO	CB	58.889	20.400	42.984	10.51
716	PRO	CG	57.757	20.889	43.873	11.89
717	PRO	CD	56.917	21.895	43.147	9.07
718	LEU	N	60.423	20.963	39.954	13.19
719	LEU	CA	60.928	20.422	38.711	14.02
720	LEU	C	61.288	18.972	38.994	13.93
721	LEU	O	61.401	18.617	40.157	12.95
722	LEU	CB	62.178	21.303	38.472	13.39
723	LEU	CG	62.181	22.123	37.185	14.69
724	LEU	CD1	62.862	23.432	37.390	13.28
725	LEU	CD2	60.808	22.403	36.589	12.21
726	PRO	N	61.492	18.060	38.006	16.81

727	PRO	CA	61.666	16.641	38.394	17.34
728	PRO	C	62.962	16.281	39.104	16.85
729	PRO	O	63.122	15.247	39.688	18.24
730	PRO	CB	61.517	15.864	37.116	17.12
731	PRO	CG	60.922	16.848	36.100	19.47
732	PRO	CD	61.300	18.261	36.556	16.45
733	ASN	N	63.900	17.198	39.011	15.30
734	ASN	CA	65.204	16.949	39.638	14.86
735	ASN	C	65.487	17.673	40.952	15.36
736	ASN	O	66.603	17.703	41.410	15.84
737	ASN	CB	66.197	17.452	38.620	14.48
738	ASN	CG	65.975	18.909	38.203	16.03
739	ASN	OD1	65.058	19.216	37.443	19.68
740	ASN	ND2	66.878	19.774	38.721	15.67
741	THR	N	64.484	18.374	41.425	15.02
742	THR	CA	64.442	19.135	42.712	12.29
743	THR	C	63.211	18.662	43.532	11.96
744	THR	O	62.712	19.350	44.385	11.69
745	THR	CB	64.049	20.608	42.328	10.87
746	THR	OG1	62.724	20.721	41.769	10.92
747	THR	CG2	64.891	21.218	41.196	10.49
748	CYS	N	62.634	17.505	43.321	14.04
749	CYS	CA	61.483	17.193	44.179	14.17
750	CYS	C	62.088	16.768	45.539	12.97
751	CYS	O	61.464	16.855	46.615	13.90
752	CYS	CB	60.644	16.031	43.646	13.16
753	CYS	SG	59.565	16.488	42.264	15.24
754	GLY	N	63.405	16.394	45.404	13.25
755	GLY	CA	64.191	15.974	46.563	14.11
756	GLY	C	64.788	17.158	47.402	14.77
757	GLY	O	64.846	17.059	48.598	15.71
758	HIS	N	65.185	18.303	46.789	15.04
759	HIS	CA	65.415	19.657	47.379	13.49
760	HIS	C	64.101	20.265	47.972	14.38
761	HIS	O	64.083	20.721	49.105	15.19
762	HIS	CB	65.898	20.682	46.344	12.89
763	HIS	CG	67.036	20.181	45.457	14.63
764	HIS	ND1	67.075	20.421	44.117	13.48
765	HIS	CD2	68.117	19.333	45.753	16.55
766	HIS	CE1	68.090	19.729	43.613	14.33
767	HIS	NE2	68.744	19.084	44.580	15.87
768	PHE	N	62.967	20.201	47.261	12.72
769	PHE	CA	61.732	20.613	47.958	12.68
770	PHE	C	61.548	19.898	49.353	13.22
771	PHE	O	61.483	20.497	50.423	12.12
772	PHE	CB	60.586	20.347	46.968	12.82

773	PHE	CG	59.235	20.806	47.480	9.60
774	PHE	CD1	58.367	19.945	48.151	8.18
775	PHE	CD2	58.819	22.104	47.261	8.54
776	PHE	CE1	57.135	20.383	48.629	11.79
777	PHE	CE2	57.551	22.497	47.662	11.03
778	PHE	CZ	56.712	21.647	48.354	10.70
779	TRP	N	61.531	18.566	49.377	12.17
780	TRP	CA	61.277	17.960	50.667	12.15
781	TRP	C	62.426	18.110	51.675	12.77
782	TRP	O	62.267	17.797	52.824	12.89
783	TRP	CB	60.914	16.499	50.457	13.28
784	TRP	CG	59.487	16.421	49.968	13.46
785	TRP	CD1	59.176	16.003	48.715	13.99
786	TRP	CD2	58.238	16.857	50.571	12.69
787	TRP	NE1	57.858	16.174	48.514	13.76
788	TRP	CE2	57.224	16.674	49.611	12.21
789	TRP	CE3	57.892	17.354	51.835	11.54
790	TRP	CZ2	55.928	17.024	49.845	11.49
791	TRP	CZ3	56.569	17.707	52.119	12.46
792	TRP	CH2	55.598	17.545	51.099	11.61
793	GLU	N	63.588	18.588	51.263	13.48
794	GLU	CA	64.731	18.763	52.162	12.78
795	GLU	C	64.458	20.064	52.881	13.54
796	GLU	O	64.488	20.065	54.123	13.56
797	GLU	CB	66.084	18.779	51.401	11.88
798	GLU	CG	67.269	19.356	52.235	15.11
799	GLU	CD	68.554	19.518	51.499	17.43
800	GLU	OE1	68.577	19.290	50.284	19.12
801	GLU	OE2	69.547	19.872	52.101	19.81
802	MET	N	63.973	21.049	51.994	11.71
803	MET	CA	63.546	22.379	52.486	12.23
804	MET	C	62.389	22.312	53.511	11.68
805	MET	O	62.291	22.943	54.555	11.24
806	MET	CB	63.108	23.239	51.328	9.82
807	MET	CG	62.214	24.420	51.724	11.63
808	MET	SD	61.999	25.602	50.392	15.04
809	MET	CE	60.555	24.934	49.564	11.38
810	VAL	N	61.422	21.461	53.168	12.17
811	VAL	CA	60.354	21.227	54.164	10.63
812	VAL	C	60.941	20.624	55.438	13.77
813	VAL	O	60.589	21.011	56.523	14.26
814	VAL	CB	59.220	20.388	53.522	10.58
815	VAL	CG1	58.576	21.226	52.398	8.22
816	VAL	CG2	58.132	19.960	54.487	10.48
817	TRP	N	61.857	19.696	55.332	13.52
818	TRP	CA	62.368	19.071	56.546	14.59

819	TRP	C	63.063	20.108	57.515	15.04
820	TRP	O	62.665	20.298	58.672	16.22
821	TRP	CB	63.263	17.908	56.111	12.97
822	TRP	CG	63.663	17.210	57.352	17.46
823	TRP	CD1	64.811	17.506	58.070	21.61
824	TRP	CD2	62.942	16.235	58.122	19.79
825	TRP	NE1	64.831	16.777	59.222	23.85
826	TRP	CE2	63.721	15.974	59.290	22.70
827	TRP	CE3	61.749	15.593	57.954	21.09
828	TRP	CZ2	63.300	15.074	60.220	21.76
829	TRP	CZ3	61.323	14.679	58.916	21.15
830	TRP	CH2	62.094	14.409	60.031	21.23
831	GLU	N	64.079	20.742	56.935	16.06
832	GLU	CA	65.024	21.609	57.615	15.05
833	GLU	C	64.396	22.880	58.008	16.50
834	GLU	O	64.758	23.461	59.019	18.37
835	GLU	CB	66.099	21.948	56.599	13.43
836	GLU	CG	66.738	20.660	56.125	13.77
837	GLU	CD	67.820	20.935	55.146	14.43
838	GLU	OE1	67.899	22.007	54.586	15.87
839	GLU	OE2	68.632	20.038	54.975	15.61
840	GLN	N	63.390	23.283	57.230	14.99
841	GLN	CA	62.612	24.477	57.635	14.10
842	GLN	C	61.510	24.226	58.676	14.79
843	GLN	O	60.879	25.146	59.160	14.03
844	GLN	CB	62.048	25.170	56.347	13.84
845	GLN	CG	63.212	25.595	55.375	14.77
846	GLN	CD	64.194	26.544	56.098	20.12
847	GLN	OE1	63.694	27.506	56.665	21.85
848	GLN	NE2	65.471	26.331	56.071	18.11
849	LYS	N	61.251	22.954	59.012	14.24
850	LYS	CA	60.227	22.483	59.980	15.01
851	LYS	C	58.797	22.890	59.696	12.96
852	LYS	O	57.994	22.992	60.604	13.31
853	LYS	CB	60.584	22.912	61.402	19.21
854	LYS	CG	62.055	22.609	61.711	21.85
855	LYS	CD	62.235	22.379	63.198	29.47
856	LYS	CE	63.661	22.216	63.640	31.82
857	LYS	NZ	64.341	23.105	62.727	37.86
858	SER	N	58.495	23.079	58.406	14.72
859	SER	CA	57.092	23.282	58.019	14.22
860	SER	C	56.246	22.042	58.300	15.12
861	SER	O	56.655	20.897	58.189	14.48
862	SER	CB	57.124	23.649	56.489	12.78
863	SER	OG	58.109	24.701	56.039	13.54
864	ARG	N	55.046	22.316	58.638	13.87

865	ARG	CA	53.889	21.469	58.787	14.62
866	ARG	C	52.900	21.380	57.558	14.77
867	ARG	O	52.279	20.349	57.295	13.72
868	ARG	CB	53.162	22.084	59.989	14.39
869	ARG	CG	52.448	21.021	60.790	23.02
870	ARG	CD	51.000	20.993	60.443	27.49
871	ARG	NE	50.286	20.242	61.462	30.20
872	ARG	CZ	50.380	18.916	61.522	29.90
873	ARG	NH1	51.307	18.211	60.950	31.36
874	ARG	NH2	49.427	18.304	62.133	30.49
875	GLY	N	52.739	22.450	56.827	15.17
876	GLY	CA	51.776	22.626	55.799	13.10
877	GLY	C	52.462	22.850	54.485	12.93
878	GLY	O	53.449	23.538	54.399	12.18
879	VAL	N	51.894	22.272	53.426	13.38
880	VAL	CA	52.274	22.713	52.082	10.87
881	VAL	C	50.983	23.124	51.461	9.66
882	VAL	O	50.002	22.387	51.541	10.04
883	VAL	CB	52.870	21.528	51.228	10.73
884	VAL	CG1	54.155	20.840	51.773	11.72
885	VAL	CG2	53.136	21.897	49.737	10.72
886	VAL	N	51.007	24.297	50.825	8.51
887	VAL	CA	49.805	24.732	50.087	7.91
888	VAL	C	50.113	24.799	48.608	8.39
889	VAL	O	50.967	25.546	48.186	9.71
890	VAL	CB	49.346	26.112	50.615	6.14
891	VAL	CG1	48.848	26.046	52.098	7.70
892	VAL	CG2	48.214	26.748	49.800	6.32
893	MET	N	49.389	24.005	47.841	8.82
894	MET	CA	49.534	23.899	46.386	8.53
895	MET	C	48.365	24.505	45.638	9.29
896	MET	O	47.289	23.983	45.711	9.66
897	MET	CB	49.534	22.412	46.115	8.63
898	MET	CG	49.584	22.144	44.622	9.02
899	MET	SD	50.458	20.629	44.313	13.59
900	MET	CE	50.211	20.435	42.521	7.30
901	LEU	N	48.591	25.598	44.954	8.05
902	LEU	CA	47.428	26.275	44.340	6.79
903	LEU	C	47.172	26.020	42.785	8.29
904	LEU	O	46.566	26.877	42.182	8.17
905	LEU	CB	47.688	27.800	44.449	8.82
906	LEU	CG	47.991	28.331	45.842	9.33
907	LEU	CD1	46.842	28.070	46.813	6.68
908	LEU	CD2	48.214	29.832	45.771	8.69
909	ASN	N	47.920	25.017	42.200	8.85
910	ASN	CA	48.020	24.702	40.735	10.85

911	ASN	C	47.769	23.175	40.514	10.96
912	ASN	O	48.012	22.421	41.451	11.52
913	ASN	CB	49.393	25.060	40.117	10.56
914	ASN	CG	50.568	24.084	40.487	10.18
915	ASN	OD1	51.127	23.276	39.749	13.30
916	ASN	ND2	51.129	24.353	41.654	6.84
917	ARG	N	47.424	22.750	39.274	12.81
918	ARG	CA	47.423	21.308	38.970	12.84
919	ARG	C	48.776	20.954	38.393	13.06
920	ARG	O	49.452	21.835	37.869	13.72
921	ARG	CB	46.231	20.948	38.085	15.06
922	ARG	CG	44.960	21.740	38.453	23.73
923	ARG	CD	43.614	21.096	38.015	34.40
924	ARG	NE	43.483	20.691	36.595	44.56
925	ARG	CZ	43.334	21.619	35.619	51.42
926	ARG	NH1	43.467	22.892	35.787	54.99
927	ARG	NH2	42.994	21.256	34.403	53.99
928	VAL	N	49.195	19.695	38.452	13.43
929	VAL	CA	50.346	19.256	37.704	16.12
930	VAL	C	50.278	19.565	36.147	16.48
931	VAL	O	51.114	20.226	35.584	14.56
932	VAL	CB	50.559	17.783	38.070	14.79
933	VAL	CG1	50.930	17.661	39.553	14.80
934	VAL	CG2	51.639	17.182	37.160	16.58
935	MET	N	49.229	19.073	35.453	17.62
936	MET	CA	48.799	19.616	34.173	19.41
937	MET	C	47.577	20.606	34.287	17.22
938	MET	O	46.471	20.315	34.733	16.41
939	MET	CB	48.548	18.474	33.180	22.53
940	MET	CG	48.920	18.893	31.711	30.44
941	MET	SD	48.488	17.626	30.498	36.43
942	MET	CE	46.891	18.345	30.183	32.23
943	GLU	N	47.925	21.768	33.762	17.49
944	GLU	CA	47.082	22.928	33.568	18.64
945	GLU	C	47.552	23.550	32.237	17.88
946	GLU	O	48.753	23.611	31.959	18.32
947	GLU	CB	47.409	24.092	34.512	16.54
948	GLU	CG	47.652	23.731	35.929	16.82
949	GLU	CD	47.619	24.979	36.772	15.94
950	GLU	OE1	48.517	25.821	36.630	15.52
951	GLU	OE2	46.727	25.093	37.611	15.98
952	LYS	N	46.605	23.992	31.444	19.17
953	LYS	CA	46.693	24.610	30.148	20.14
954	LYS	C	47.513	23.739	29.202	18.74
955	LYS	O	48.351	24.244	28.449	18.86
956	LYS	CB	47.304	25.984	30.368	21.50

957	LYS	CG	46.267	26.889	31.035	24.11
958	LYS	CD	46.770	28.322	31.089	28.82
959	LYS	CE	45.657	29.354	31.107	30.30
960	LYS	NZ	44.532	28.741	31.820	32.58
961	GLY	N	47.273	22.392	29.319	18.79
962	GLY	CA	47.911	21.493	28.344	17.83
963	GLY	C	49.363	21.124	28.602	19.02
964	GLY	O	49.889	20.163	28.022	18.80
965	SER	N	49.994	21.951	29.434	16.08
966	SER	CA	51.417	21.727	29.690	17.76
967	SER	C	51.563	21.319	31.153	16.07
968	SER	O	50.624	21.508	31.921	15.80
969	SER	CB	52.195	22.984	29.281	21.32
970	SER	OG	51.454	23.745	28.215	29.95
971	LEU	N	52.706	20.665	31.433	16.19
972	LEU	CA	53.044	20.095	32.721	14.22
973	LEU	C	53.814	21.162	33.523	14.90
974	LEU	O	54.937	21.513	33.212	16.30
975	LEU	CB	53.928	18.847	32.505	13.16
976	LEU	CG	53.098	17.636	32.063	12.66
977	LEU	CD1	52.255	17.105	33.249	15.43
978	LEU	CD2	53.993	16.510	31.569	13.88
979	LYS	N	53.070	21.738	34.484	14.30
980	LYS	CA	53.355	22.962	35.234	11.19
981	LYS	C	54.103	22.727	36.555	10.51
982	LYS	O	54.480	23.691	37.202	11.24
983	LYS	CB	51.969	23.563	35.492	11.90
984	LYS	CG	51.377	24.141	34.173	15.22
985	LYS	CD	52.251	25.323	33.894	16.86
986	LYS	CE	51.945	26.341	32.815	20.26
987	LYS	NZ	52.785	27.477	33.270	18.45
988	CYS	N	54.265	21.458	36.919	10.35
989	CYS	CA	54.800	21.085	38.199	10.12
990	CYS	C	55.093	19.570	38.124	13.34
991	CYS	O	54.346	18.872	37.449	13.61
992	CYS	CB	53.752	21.438	39.298	13.04
993	CYS	SG	54.171	21.096	41.056	11.06
994	ALA	N	56.092	19.102	38.912	11.84
995	ALA	CA	56.384	17.664	39.115	11.47
996	ALA	C	55.350	16.986	39.954	13.20
997	ALA	O	54.725	17.565	40.853	10.87
998	ALA	CB	57.698	17.551	39.874	9.90
999	GLN	N	55.227	15.685	39.755	12.25
1000	GLN	CA	54.380	14.965	40.731	13.18
1001	GLN	C	55.285	14.601	41.907	13.71
1002	GLN	O	55.974	13.592	41.922	14.92

1003	GLN	CB	53.719	13.735	40.112	13.64
1004	GLN	CG	52.758	12.973	41.060	14.19
1005	GLN	CD	51.427	13.725	41.216	14.78
1006	GLN	OE1	50.905	13.910	42.309	20.52
1007	GLN	NE2	50.901	14.217	40.086	13.59
1008	TYR	N	55.306	15.502	42.891	12.19
1009	TYR	CA	56.373	15.447	43.967	11.14
1010	TYR	C	55.940	14.903	45.328	10.72
1011	TYR	O	56.779	14.953	46.207	12.61
1012	TYR	CB	56.928	16.825	44.297	10.70
1013	TYR	CG	55.892	17.745	44.873	12.19
1014	TYR	CD1	55.710	17.845	46.233	10.21
1015	TYR	CD2	55.141	18.558	44.050	11.16
1016	TYR	CE1	54.801	18.729	46.793	12.37
1017	TYR	CE2	54.213	19.435	44.555	10.83
1018	TYR	CZ	54.033	19.497	45.943	11.09
1019	TYR	OH	53.050	20.302	46.488	11.70
1020	TRP	N	54.662	14.460	45.484	11.94
1021	TRP	CA	54.108	13.696	46.608	12.84
1022	TRP	C	53.453	12.393	46.058	14.59
1023	TRP	O	53.073	12.404	44.901	14.57
1024	TRP	CB	53.090	14.582	47.358	12.85
1025	TRP	CG	51.796	14.668	46.559	13.65
1026	TRP	CD1	50.660	13.882	46.775	14.58
1027	TRP	CD2	51.462	15.520	45.460	12.43
1028	TRP	NE1	49.663	14.196	45.908	14.02
1029	TRP	CE2	50.123	15.214	45.098	12.63
1030	TRP	CE3	52.186	16.429	44.734	13.32
1031	TRP	CZ2	49.544	15.874	44.043	12.31
1032	TRP	CZ3	51.623	17.068	43.649	11.49
1033	TRP	CH2	50.298	16.797	43.312	14.96
1034	PRO	N	53.291	11.284	46.898	16.00
1035	PRO	CA	52.633	10.039	46.450	15.76
1036	PRO	C	51.096	10.056	46.250	16.40
1037	PRO	O	50.249	10.513	47.021	18.51
1038	PRO	CB	53.112	8.965	47.400	12.06
1039	PRO	CG	53.352	9.784	48.636	15.79
1040	PRO	CD	53.814	11.162	48.256	15.75
1041	GLN	N	50.762	9.495	45.124	18.99
1042	GLN	CA	49.356	9.444	44.808	21.65
1043	GLN	C	48.588	8.192	45.388	22.14
1044	GLN	O	47.377	8.070	45.250	20.49
1045	GLN	CB	49.477	9.419	43.309	26.00
1046	GLN	CG	49.582	10.837	42.765	32.71
1047	GLN	CD	49.147	10.778	41.328	36.57
1048	GLN	OE1	49.811	10.217	40.486	35.28

1049	GLN	NE2	47.927	11.228	41.111	40.87
1050	LYS	N	49.312	7.229	46.019	20.39
1051	LYS	CA	48.578	6.239	46.799	19.10
1052	LYS	C	49.447	5.480	47.773	16.46
1053	LYS	O	50.649	5.374	47.569	16.58
1054	LYS	CB	48.004	5.271	45.819	22.59
1055	LYS	CG	49.022	4.477	44.999	24.94
1056	LYS	CD	48.247	3.613	44.031	30.53
1057	LYS	CE	46.873	4.187	43.585	32.07
1058	LYS	NZ	46.151	3.195	42.750	40.14
1059	GLU	N	48.770	4.939	48.805	15.88
1060	GLU	CA	49.282	4.619	50.076	15.37
1061	GLU	C	50.274	3.498	49.993	15.69
1062	GLU	O	51.310	3.575	50.666	13.68
1063	GLU	CB	48.129	4.329	50.969	16.72
1064	GLU	CG	47.224	5.504	51.264	14.29
1065	GLU	CD	46.086	5.726	50.288	18.80
1066	GLU	OE1	46.254	5.591	49.071	21.62
1067	GLU	OE2	44.996	6.034	50.720	21.27
1068	GLU	N	50.001	2.488	49.145	18.42
1069	GLU	CA	50.982	1.369	48.868	20.95
1070	GLU	C	52.285	1.728	48.121	20.76
1071	GLU	O	53.234	0.936	48.094	20.49
1072	GLU	CB	50.407	0.309	47.934	20.78
1073	GLU	CG	48.890	0.282	47.935	25.93
1074	GLU	CD	48.253	1.097	46.847	25.99
1075	GLU	OE1	48.672	0.948	45.699	28.63
1076	GLU	OE2	47.378	1.916	47.165	25.53
1077	LYS	N	52.277	2.922	47.470	21.38
1078	LYS	CA	53.466	3.451	46.700	21.50
1079	LYS	C	54.120	4.756	47.250	21.97
1080	LYS	O	53.847	5.847	46.775	22.57
1081	LYS	CB	53.121	3.583	45.211	22.92
1082	LYS	CG	53.120	2.175	44.507	27.23
1083	LYS	CD	53.566	1.981	43.052	35.59
1084	LYS	CE	54.901	2.700	42.698	43.39
1085	LYS	NZ	56.064	2.530	43.615	46.48
1086	GLU	N	54.995	4.585	48.246	21.26
1087	GLU	CA	55.858	5.703	48.687	22.94
1088	GLU	C	56.922	6.019	47.618	21.77
1089	GLU	O	57.224	5.216	46.703	23.33
1090	GLU	CB	56.631	5.472	50.033	22.83
1091	GLU	CG	56.303	4.151	50.740	28.82
1092	GLU	CD	56.755	2.950	49.946	29.12
1093	GLU	OE1	57.947	2.882	49.726	33.37
1094	GLU	OE2	55.910	2.091	49.582	28.44

1095	MET	N	57.395	7.255	47.918	18.83
1096	MET	CA	58.502	7.859	47.186	17.54
1097	MET	C	59.720	7.939	48.072	19.07
1098	MET	O	59.583	8.268	49.240	20.58
1099	MET	CB	58.083	9.281	46.771	16.27
1100	MET	CG	57.088	9.220	45.629	16.56
1101	MET	SD	56.497	10.824	45.225	19.88
1102	MET	CE	57.882	11.386	44.232	18.70
1103	ILE	N	60.896	7.720	47.557	18.63
1104	ILE	CA	62.108	7.877	48.322	20.60
1105	ILE	C	63.025	8.809	47.514	20.37
1106	ILE	O	63.395	8.568	46.393	23.05
1107	ILE	CB	62.691	6.493	48.661	24.01
1108	ILE	CG1	61.881	5.871	49.811	25.81
1109	ILE	CG2	64.181	6.578	49.065	24.90
1110	ILE	CD1	61.992	4.357	49.909	27.88
1111	PHE	N	63.380	9.944	48.145	19.97
1112	PHE	CA	64.224	10.949	47.503	18.46
1113	PHE	C	65.685	10.633	47.905	19.73
1114	PHE	O	66.114	10.938	49.001	18.94
1115	PHE	CB	63.753	12.370	47.917	16.35
1116	PHE	CG	62.290	12.582	47.628	14.87
1117	PHE	CD1	61.851	12.931	46.357	13.55
1118	PHE	CD2	61.348	12.399	48.607	16.14
1119	PHE	CE1	60.511	13.044	46.035	14.72
1120	PHE	CE2	60.000	12.519	48.297	14.63
1121	PHE	CZ	59.565	12.811	47.004	14.92
1122	GLU	N	66.423	9.955	47.009	23.42
1123	GLU	CA	67.730	9.355	47.371	27.04
1124	GLU	C	68.809	10.381	47.518	26.67
1125	GLU	O	69.611	10.299	48.440	27.77
1126	GLU	CB	68.229	8.253	46.431	32.84
1127	GLU	CG	67.362	6.947	46.395	43.59
1128	GLU	CD	68.029	5.711	45.646	52.36
1129	GLU	OE1	68.362	5.845	44.439	54.69
1130	GLU	OE2	68.199	4.647	46.298	55.07
1131	ASP	N	68.765	11.386	46.636	25.27
1132	ASP	CA	69.664	12.544	46.813	24.77
1133	ASP	C	69.573	13.322	48.180	24.82
1134	ASP	O	70.550	13.880	48.657	26.69
1135	ASP	CB	69.487	13.507	45.649	25.87
1136	ASP	CG	68.195	14.296	45.612	28.11
1137	ASP	OD1	67.142	13.727	45.835	27.95
1138	ASP	OD2	68.296	15.481	45.365	30.09
1139	THR	N	68.365	13.360	48.766	22.69
1140	THR	CA	68.270	13.979	50.054	20.10

1141	THR	C	67.933	13.020	51.178	20.10
1142	THR	O	67.943	13.373	52.347	20.15
1143	THR	CB	67.476	15.268	50.010	18.17
1144	THR	OG1	66.041	14.985	49.980	15.16
1145	THR	CG2	68.214	16.309	49.052	16.50
1146	ASN	N	67.735	11.756	50.863	21.38
1147	ASN	CA	67.628	10.783	51.969	23.28
1148	ASN	C	66.346	10.889	52.861	23.35
1149	ASN	O	66.353	10.887	54.078	24.28
1150	ASN	CB	68.918	10.815	52.831	27.97
1151	ASN	CG	69.285	9.445	53.414	32.19
1152	ASN	OD1	68.963	8.394	52.899	34.42
1153	ASN	ND2	70.048	9.471	54.465	31.14
1154	LEU	N	65.246	10.944	52.152	22.74
1155	LEU	CA	63.923	11.233	52.687	21.67
1156	LEU	C	62.917	10.253	52.009	20.94
1157	LEU	O	62.978	9.941	50.835	21.39
1158	LEU	CB	63.586	12.665	52.212	21.84
1159	LEU	CG	63.600	13.787	53.240	23.27
1160	LEU	CD1	64.055	15.113	52.656	17.13
1161	LEU	CD2	64.224	13.472	54.596	21.62
1162	LYS	N	61.974	9.802	52.783	21.10
1163	LYS	CA	60.920	8.934	52.328	19.53
1164	LYS	C	59.609	9.681	52.550	18.34
1165	LYS	O	59.486	10.402	53.520	20.22
1166	LYS	CB	61.135	7.645	53.185	20.94
1167	LYS	CG	59.973	6.657	53.250	22.87
1168	LYS	CD	60.414	5.282	53.669	29.27
1169	LYS	CE	59.161	4.429	53.683	32.16
1170	LYS	NZ	59.380	3.130	54.360	36.84
1171	LEU	N	58.659	9.543	51.618	16.41
1172	LEU	CA	57.406	10.345	51.727	16.41
1173	LEU	C	56.161	9.462	51.429	16.89
1174	LEU	O	56.112	8.863	50.367	16.71
1175	LEU	CB	57.542	11.526	50.777	15.09
1176	LEU	CG	56.271	12.369	50.729	13.98
1177	LEU	CD1	56.382	13.211	49.453	15.42
1178	LEU	CD2	56.090	13.271	51.990	16.75
1179	THR	N	55.183	9.368	52.377	17.65
1180	THR	CA	54.124	8.352	52.362	17.51
1181	THR	C	52.766	9.036	52.409	16.95
1182	THR	O	52.566	9.943	53.206	16.10
1183	THR	CB	54.424	7.325	53.497	15.94
1184	THR	OG1	55.871	7.204	53.749	15.73
1185	THR	CG2	54.295	5.897	53.009	17.67
1186	LEU	N	51.815	8.672	51.504	15.85

1187	LEU	CA	50.464	9.240	51.601	16.51
1188	LEU	C	49.849	8.492	52.784	19.83
1189	LEU	O	49.757	7.284	52.720	20.59
1190	LEU	CB	49.614	9.054	50.317	15.58
1191	LEU	CG	48.211	9.745	50.328	15.08
1192	LEU	CD1	47.345	9.428	49.092	13.12
1193	LEU	CD2	48.368	11.251	50.477	15.75
1194	ILE	N	49.561	9.233	53.881	18.46
1195	ILE	CA	48.795	8.626	54.964	18.30
1196	ILE	C	47.299	8.487	54.699	18.81
1197	ILE	O	46.786	7.492	55.168	19.41
1198	ILE	CB	49.008	9.309	56.286	17.44
1199	ILE	CG1	50.497	9.177	56.670	16.16
1200	ILE	CG2	48.030	8.763	57.336	17.37
1201	ILE	CD1	51.109	7.804	56.438	15.26
1202	SER	N	46.772	9.561	54.052	18.02
1203	SER	CA	45.404	9.579	53.498	19.40
1204	SER	C	45.002	10.838	52.741	21.38
1205	SER	O	45.731	11.814	52.767	22.64
1206	SER	CB	44.410	9.580	54.635	21.28
1207	SER	OG	44.258	10.789	55.488	24.51
1208	GLU	N	43.804	10.869	52.157	22.91
1209	GLU	CA	43.247	12.165	51.666	25.57
1210	GLU	C	41.728	12.456	51.777	25.11
1211	GLU	O	40.921	11.581	51.933	28.12
1212	GLU	CB	43.646	12.377	50.247	27.94
1213	GLU	CG	43.357	11.238	49.297	32.29
1214	GLU	CD	44.066	11.603	47.994	38.30
1215	GLU	OE1	44.307	12.793	47.744	43.02
1216	GLU	OE2	44.430	10.703	47.259	41.87
1217	ASP	N	41.337	13.722	51.692	20.31
1218	ASP	CA	39.977	14.185	51.811	18.75
1219	ASP	C	39.742	15.051	50.582	19.30
1220	ASP	O	40.185	16.193	50.485	17.85
1221	ASP	CB	40.000	14.960	53.115	21.92
1222	ASP	CG	38.796	15.833	53.455	28.13
1223	ASP	OD1	37.691	15.542	52.994	28.01
1224	ASP	OD2	38.979	16.828	54.204	33.77
1225	ILE	N	39.104	14.403	49.603	19.47
1226	ILE	CA	38.862	15.024	48.297	20.98
1227	ILE	C	37.511	15.728	48.182	22.51
1228	ILE	O	36.486	15.086	48.315	25.15
1229	ILE	CB	38.844	13.927	47.248	22.51
1230	ILE	CG1	40.112	13.113	47.366	22.32
1231	ILE	CG2	38.613	14.468	45.803	23.73
1232	ILE	CD1	40.193	12.123	46.229	22.61

1233	LYS	N	37.553	17.021	47.906	21.11
1234	LYS	CA	36.359	17.863	47.866	20.45
1235	LYS	C	36.188	18.316	46.391	20.80
1236	LYS	O	37.064	18.038	45.587	22.26
1237	LYS	CB	36.663	18.921	48.924	22.37
1238	LYS	CG	36.755	18.276	50.320	25.62
1239	LYS	CD	35.354	18.201	50.911	29.83
1240	LYS	CE	35.212	17.510	52.277	33.05
1241	LYS	NZ	33.797	17.735	52.656	35.32
1242	THR	N	35.094	18.956	45.972	19.82
1243	THR	CA	34.963	19.315	44.853	21.59
1244	THR	C	35.971	20.151	44.101	20.83
1245	THR	O	36.245	19.955	42.922	22.59
1246	THR	CB	33.646	20.055	44.669	24.13
1247	THR	OG1	33.609	21.266	45.395	24.73
1248	THR	CG2	32.537	19.144	45.139	30.44
1249	TYR	N	36.550	21.088	44.859	17.73
1250	TYR	CA	37.522	21.987	44.234	15.97
1251	TYR	C	38.926	22.037	44.888	15.46
1252	TYR	O	39.790	22.830	44.552	15.86
1253	TYR	CB	36.862	23.362	44.168	12.55
1254	TYR	CG	36.787	24.053	45.510	12.56
1255	TYR	CD1	35.748	23.758	46.416	14.70
1256	TYR	CD2	37.745	25.026	45.793	14.86
1257	TYR	CE1	35.638	24.506	47.593	15.48
1258	TYR	CE2	37.676	25.747	47.000	16.69
1259	TYR	CZ	36.598	25.497	47.858	16.96
1260	TYR	OH	36.474	26.267	48.979	15.71
1261	TYR	N	39.089	21.152	45.889	14.74
1262	TYR	CA	40.333	21.010	46.643	14.03
1263	TYR	C	40.453	19.639	47.315	16.12
1264	TYR	O	39.469	18.949	47.536	17.82
1265	TYR	CB	40.575	22.195	47.613	12.74
1266	TYR	CG	39.769	22.161	48.905	15.40
1267	TYR	CD1	40.334	21.536	50.033	13.77
1268	TYR	CD2	38.479	22.734	48.947	18.58
1269	TYR	CE1	39.560	21.424	51.207	15.81
1270	TYR	CE2	37.715	22.646	50.134	17.84
1271	TYR	CZ	38.266	21.965	51.235	16.69
1272	TYR	OH	37.544	21.811	52.389	18.92
1273	THR	N	41.697	19.226	47.627	14.21
1274	THR	CA	41.956	17.974	48.377	15.42
1275	THR	C	42.951	18.234	49.465	15.44
1276	THR	O	43.955	18.887	49.248	15.14
1277	THR	CB	42.630	16.919	47.491	16.15
1278	THR	OG1	41.761	16.554	46.440	16.75

1279	THR	CG2	43.128	15.643	48.159	15.21
1280	VAL	N	42.638	17.716	50.607	14.25
1281	VAL	CA	43.604	17.716	51.687	15.61
1282	VAL	C	44.212	16.325	51.849	15.76
1283	VAL	O	43.534	15.320	51.815	16.87
1284	VAL	CB	42.971	18.215	53.028	15.56
1285	VAL	CG1	42.210	19.534	52.861	17.93
1286	VAL	CG2	44.018	18.329	54.147	15.84
1287	ARG	N	45.545	16.296	51.981	15.23
1288	ARG	CA	46.259	15.034	52.198	12.90
1289	ARG	C	47.094	15.095	53.452	14.57
1290	ARG	O	47.669	16.099	53.852	14.51
1291	ARG	CB	47.213	14.689	51.060	12.22
1292	ARG	CG	46.431	14.664	49.771	14.22
1293	ARG	CD	47.328	14.307	48.603	17.43
1294	ARG	NE	46.522	14.288	47.372	19.70
1295	ARG	CZ	46.343	15.286	46.563	18.02
1296	ARG	NH1	46.936	16.433	46.719	20.75
1297	ARG	NH2	45.562	15.101	45.583	22.30
1298	GLN	N	47.167	13.949	54.075	15.95
1299	GLN	CA	48.177	13.855	55.083	15.20
1300	GLN	C	49.286	12.980	54.578	14.98
1301	GLN	O	49.094	11.915	54.000	15.16
1302	GLN	CB	47.425	13.295	56.248	19.99
1303	GLN	CG	48.352	12.986	57.366	24.39
1304	GLN	CD	47.446	12.294	58.357	33.29
1305	GLN	OE1	46.290	11.917	58.100	36.18
1306	GLN	NE2	48.061	12.057	59.508	32.20
1307	LEU	N	50.472	13.510	54.813	14.40
1308	LEU	CA	51.690	12.890	54.351	16.50
1309	LEU	C	52.629	12.588	55.537	17.55
1310	LEU	O	52.702	13.268	56.555	18.19
1311	LEU	CB	52.425	13.840	53.397	16.87
1312	LEU	CG	52.057	14.029	51.920	19.16
1313	LEU	CD1	52.220	15.473	51.494	18.62
1314	LEU	CD2	50.780	13.408	51.439	19.45
1315	GLU	N	53.373	11.519	55.358	16.26
1316	GLU	CA	54.428	11.311	56.300	16.63
1317	GLU	C	55.754	11.455	55.632	15.84
1318	GLU	O	56.066	10.787	54.676	17.35
1319	GLU	CB	54.304	9.947	56.958	17.38
1320	GLU	CG	55.477	9.848	57.928	23.65
1321	GLU	CD	55.430	8.583	58.764	30.56
1322	GLU	OE1	54.547	8.475	59.626	31.25
1323	GLU	OE2	56.295	7.734	58.553	32.96
1324	LEU	N	56.529	12.352	56.152	17.81

1325	LEU	CA	57.907	12.582	55.715	19.00
1326	LEU	C	58.902	11.990	56.739	21.54
1327	LEU	O	59.000	12.436	57.883	19.81
1328	LEU	CB	58.084	14.121	55.646	17.55
1329	LEU	CG	59.011	14.839	54.653	19.65
1330	LEU	CD1	59.999	13.982	53.910	20.83
1331	LEU	CD2	59.611	16.118	55.230	17.35
1332	GLU	N	59.677	11.018	56.242	24.40
1333	GLU	CA	60.757	10.444	57.062	24.80
1334	GLU	C	62.183	10.790	56.622	25.64
1335	GLU	O	62.666	10.593	55.508	24.49
1336	GLU	CB	60.566	8.923	57.182	24.55
1337	GLU	CG	61.533	8.201	58.134	26.49
1338	GLU	CD	61.368	6.701	58.012	28.97
1339	GLU	OE1	60.447	6.223	57.350	33.55
1340	GLU	OE2	62.199	5.969	58.536	32.02
1341	ASN	N	62.873	11.339	57.617	26.33
1342	ASN	CA	64.303	11.526	57.452	28.36
1343	ASN	C	65.008	10.195	57.582	29.60
1344	ASN	O	65.247	9.741	58.682	31.34
1345	ASN	CB	64.793	12.543	58.488	27.93
1346	ASN	CG	66.295	12.759	58.412	30.21
1347	ASN	OD1	67.105	11.921	58.046	28.62
1348	ASN	ND2	66.668	13.937	58.851	31.76
1349	LEU	N	65.339	9.597	56.434	30.56
1350	LEU	CA	65.970	8.276	56.397	31.30
1351	LEU	C	67.360	8.191	57.066	35.28
1352	LEU	O	67.827	7.146	57.488	35.62
1353	LEU	CB	66.080	7.880	54.942	28.95
1354	LEU	CG	65.153	6.811	54.458	29.38
1355	LEU	CD1	65.096	6.740	52.927	27.85
1356	LEU	CD2	63.794	6.896	55.086	30.00
1357	THR	N	68.009	9.367	57.192	37.71
1358	THR	CA	69.278	9.474	57.935	41.16
1359	THR	C	69.130	9.189	59.443	43.17
1360	THR	O	70.010	8.733	60.157	45.18
1361	THR	CB	69.921	10.888	57.739	44.16
1362	THR	OG1	70.079	11.267	56.353	45.45
1363	THR	CG2	71.278	11.033	58.430	44.74
1364	THR	N	67.912	9.502	59.928	43.51
1365	THR	CA	67.627	9.396	61.373	40.76
1366	THR	C	66.443	8.517	61.738	41.34
1367	THR	O	66.193	8.141	62.866	43.02
1368	THR	CB	67.386	10.777	62.009	39.25
1369	THR	OG1	66.206	11.364	61.461	42.09
1370	THR	CG2	68.536	11.758	61.802	37.92

1371	GLN	N	65.653	8.252	60.722	40.94
1372	GLN	CA	64.289	7.831	61.000	41.20
1373	GLN	C	63.388	8.708	61.881	38.70
1374	GLN	O	62.322	8.304	62.315	38.13
1375	GLN	CB	64.284	6.380	61.408	45.37
1376	GLN	CG	64.898	5.645	60.250	51.51
1377	GLN	CD	64.977	4.182	60.571	56.44
1378	GLN	OE1	65.018	3.741	61.710	58.04
1379	GLN	NE2	65.051	3.403	59.497	61.09
1380	GLU	N	63.785	9.974	62.092	37.29
1381	GLU	CA	62.727	10.920	62.488	37.74
1382	GLU	C	61.627	11.026	61.422	35.73
1383	GLU	O	61.806	10.869	60.217	34.94
1384	GLU	CB	63.277	12.311	62.903	43.18
1385	GLU	CG	62.269	13.276	63.617	51.01
1386	GLU	CD	62.855	14.683	63.932	57.11
1387	GLU	OE1	64.057	14.771	64.282	59.70
1388	GLU	OE2	62.106	15.688	63.812	59.23
1389	THR	N	60.452	11.227	61.976	33.44
1390	THR	CA	59.253	11.210	61.132	31.67
1391	THR	C	58.364	12.397	61.416	30.34
1392	THR	O	58.213	12.814	62.569	31.62
1393	THR	CB	58.498	9.890	61.287	29.52
1394	THR	OG1	58.650	9.203	60.065	31.41
1395	THR	CG2	57.054	9.944	61.745	27.83
1396	ARG	N	57.809	12.940	60.314	27.40
1397	ARG	CA	56.900	14.072	60.476	22.96
1398	ARG	C	55.656	14.011	59.676	19.60
1399	ARG	O	55.670	13.570	58.544	18.08
1400	ARG	CB	57.517	15.400	60.125	24.02
1401	ARG	CG	58.772	15.656	60.892	27.06
1402	ARG	CD	59.108	17.126	60.821	30.34
1403	ARG	NE	60.299	17.280	61.631	31.08
1404	ARG	CZ	61.259	18.051	61.210	33.27
1405	ARG	NH1	61.083	18.824	60.138	28.01
1406	ARG	NH2	62.397	17.980	61.904	34.77
1407	GLU	N	54.607	14.560	60.263	19.61
1408	GLU	CA	53.391	14.722	59.470	20.49
1409	GLU	C	53.307	16.068	58.787	18.35
1410	GLU	O	53.451	17.113	59.403	19.50
1411	GLU	CB	52.147	14.576	60.334	23.73
1412	GLU	CG	50.804	14.805	59.633	30.58
1413	GLU	CD	49.709	15.110	60.669	37.37
1414	GLU	OE1	49.895	15.928	61.586	42.91
1415	GLU	OE2	48.642	14.550	60.567	39.95
1416	ILE	N	53.037	15.988	57.502	17.31

1417	ILE	CA	52.824	17.183	56.671	15.44
1418	ILE	C	51.428	17.188	56.122	13.03
1419	ILE	O	50.984	16.205	55.574	13.73
1420	ILE	CB	53.864	17.224	55.509	14.77
1421	ILE	CG1	55.351	17.051	55.964	13.99
1422	ILE	CG2	53.605	18.469	54.616	13.81
1423	ILE	CD1	56.011	18.081	56.937	13.39
1424	LEU	N	50.739	18.290	56.267	9.92
1425	LEU	CA	49.468	18.427	55.596	10.85
1426	LEU	C	49.617	19.120	54.238	12.45
1427	LEU	O	50.280	20.137	54.100	13.72
1428	LEU	CB	48.604	19.334	56.441	11.52
1429	LEU	CG	47.671	18.670	57.476	17.76
1430	LEU	CD1	47.397	19.618	58.652	14.86
1431	LEU	CD2	48.036	17.234	57.826	15.60
1432	HIS	N	48.967	18.566	53.225	10.68
1433	HIS	CA	49.032	19.147	51.860	11.55
1434	HIS	C	47.653	19.632	51.485	12.79
1435	HIS	O	46.691	18.863	51.473	14.70
1436	HIS	CB	49.509	18.015	50.917	11.04
1437	HIS	CG	49.846	18.414	49.500	9.68
1438	HIS	ND1	49.049	18.115	48.481	10.25
1439	HIS	CD2	50.975	19.042	49.048	10.64
1440	HIS	CE1	49.666	18.552	47.378	12.62
1441	HIS	NE2	50.846	19.126	47.727	11.21
1442	PHE	N	47.569	20.948	51.199	12.23
1443	PHE	CA	46.274	21.521	50.815	10.89
1444	PHE	C	46.347	21.882	49.348	13.34
1445	PHE	O	47.133	22.727	48.947	13.55
1446	PHE	CB	45.985	22.804	51.608	10.80
1447	PHE	CG	46.010	22.514	53.082	11.64
1448	PHE	CD1	47.239	22.635	53.771	11.60
1449	PHE	CD2	44.825	22.131	53.751	14.48
1450	PHE	CE1	47.320	22.342	55.132	12.91
1451	PHE	CE2	44.901	21.852	55.142	15.96
1452	PHE	CZ	46.143	21.936	55.791	13.40
1453	HIS	N	45.551	21.162	48.554	11.63
1454	HIS	CA	45.637	21.261	47.102	10.69
1455	HIS	C	44.419	21.873	46.463	11.28
1456	HIS	O	43.339	21.303	46.375	10.79
1457	HIS	CB	45.985	19.871	46.547	11.78
1458	HIS	CG	46.316	19.861	45.068	10.24
1459	HIS	ND1	46.407	20.911	44.219	13.45
1460	HIS	CD2	46.596	18.751	44.321	9.09
1461	HIS	CE1	46.724	20.470	42.970	8.49
1462	HIS	NE2	46.847	19.132	43.028	12.97

1463	TYR	N	44.598	23.139	46.037	10.13
1464	TYR	CA	43.496	23.797	45.360	11.53
1465	TYR	C	43.543	23.415	43.888	12.75
1466	TYR	O	44.543	23.620	43.217	11.94
1467	TYR	CB	43.699	25.310	45.529	12.91
1468	TYR	CG	42.453	26.186	45.414	14.41
1469	TYR	CD1	41.617	26.161	44.267	12.62
1470	TYR	CD2	42.190	27.059	46.496	14.67
1471	TYR	CE1	40.497	27.009	44.203	14.22
1472	TYR	CE2	41.062	27.896	46.437	15.77
1473	TYR	CZ	40.224	27.857	45.292	16.57
1474	TYR	OH	39.121	28.676	45.247	18.08
1475	THR	N	42.470	22.797	43.411	13.66
1476	THR	CA	42.557	22.223	42.056	14.87
1477	THR	C	41.794	22.989	40.931	16.37
1478	THR	O	41.788	22.650	39.752	19.74
1479	THR	CB	42.122	20.752	42.107	13.92
1480	THR	OG1	40.780	20.610	42.619	14.21
1481	THR	CG2	43.091	19.964	42.981	14.13
1482	THR	N	41.108	24.086	41.337	17.79
1483	THR	CA	40.223	24.849	40.406	17.71
1484	THR	C	40.545	26.343	40.315	17.22
1485	THR	O	39.717	27.169	39.955	19.49
1486	THR	CB	38.737	24.756	40.818	20.00
1487	THR	OG1	38.645	25.274	42.134	22.57
1488	THR	CG2	38.165	23.331	40.809	17.86
1489	TRP	N	41.824	26.648	40.637	13.24
1490	TRP	CA	42.325	28.014	40.474	11.42
1491	TRP	C	43.192	28.106	39.219	11.23
1492	TRP	O	44.305	27.599	39.146	13.88
1493	TRP	CB	43.175	28.346	41.714	10.59
1494	TRP	CG	43.522	29.827	41.830	10.86
1495	TRP	CD1	43.572	30.834	40.839	10.44
1496	TRP	CD2	43.944	30.486	43.029	11.23
1497	TRP	NE1	43.985	32.030	41.334	11.38
1498	TRP	CE2	44.223	31.860	42.696	11.59
1499	TRP	CE3	44.121	30.010	44.341	12.73
1500	TRP	CZ2	44.674	32.751	43.694	9.06
1501	TRP	CZ3	44.569	30.912	45.324	11.86
1502	TRP	CH2	44.846	32.248	45.002	9.08
1503	PRO	N	42.673	28.737	38.174	11.63
1504	PRO	CA	43.454	28.717	36.926	12.03
1505	PRO	C	44.752	29.544	36.926	10.91
1506	PRO	O	44.841	30.605	37.525	11.74
1507	PRO	CB	42.440	29.259	35.916	15.45
1508	PRO	CG	41.096	29.392	36.622	16.92

1509	PRO	CD	41.398	29.448	38.084	12.40
1510	ASP	N	45.746	29.023	36.201	9.83
1511	ASP	CA	46.936	29.819	36.018	13.50
1512	ASP	C	46.686	31.178	35.371	15.42
1513	ASP	O	45.875	31.324	34.474	16.15
1514	ASP	CB	47.954	29.031	35.195	14.19
1515	ASP	CG	49.381	29.475	35.461	17.10
1516	ASP	OD1	49.628	30.416	36.256	16.38
1517	ASP	OD2	50.271	28.847	34.883	16.84
1518	PHE	N	47.308	32.203	35.958	15.66
1519	PHE	CA	46.951	33.601	35.630	13.22
1520	PHE	C	45.496	34.007	35.774	13.65
1521	PHE	O	45.036	34.974	35.189	14.13
1522	PHE	CB	47.522	33.989	34.243	15.03
1523	PHE	CG	49.046	33.819	34.221	16.37
1524	PHE	CD1	49.875	34.865	34.737	12.85
1525	PHE	CD2	49.590	32.627	33.669	15.04
1526	PHE	CE1	51.275	34.714	34.723	10.54
1527	PHE	CE2	50.986	32.515	33.639	12.82
1528	PHE	CZ	51.798	33.547	34.161	12.68
1529	GLY	N	44.790	33.186	36.600	12.17
1530	GLY	CA	43.402	33.477	36.870	12.74
1531	GLY	C	43.130	33.699	38.349	13.53
1532	GLY	O	44.023	33.939	39.149	12.80
1533	VAL	N	41.854	33.622	38.691	14.29
1534	VAL	CA	41.352	33.878	40.056	13.36
1535	VAL	C	40.477	32.685	40.533	15.85
1536	VAL	O	39.970	31.920	39.707	16.84
1537	VAL	CB	40.533	35.165	40.144	12.64
1538	VAL	CG1	39.246	35.111	39.297	13.96
1539	VAL	CG2	41.357	36.379	39.842	12.56
1540	PRO	N	40.310	32.541	41.888	16.09
1541	PRO	CA	39.326	31.553	42.374	14.29
1542	PRO	C	37.904	31.850	41.841	16.70
1543	PRO	O	37.538	32.942	41.394	15.47
1544	PRO	CB	39.425	31.709	43.893	12.24
1545	PRO	CG	40.797	32.289	44.158	11.83
1546	PRO	CD	41.011	33.237	42.981	14.99
1547	GLU	N	37.091	30.811	41.895	18.37
1548	GLU	CA	35.721	30.970	41.414	20.99
1549	GLU	C	34.895	32.053	42.123	22.01
1550	GLU	O	34.014	32.699	41.571	24.26
1551	GLU	CB	34.978	29.614	41.414	22.54
1552	GLU	CG	35.941	28.443	41.162	31.50
1553	GLU	CD	36.522	27.764	42.465	36.66
1554	GLU	OE1	37.244	28.386	43.315	31.28

1555	GLU	OE2	36.201	26.562	42.601	36.17
1556	SER	N	35.218	32.225	43.432	20.38
1557	SER	CA	34.520	33.218	44.274	17.88
1558	SER	C	35.369	33.535	45.449	15.08
1559	SER	O	36.146	32.701	45.885	14.67
1560	SER	CB	33.107	32.739	44.793	16.14
1561	SER	OG	33.172	31.454	45.419	13.25
1562	PRO	N	35.198	34.731	46.003	17.02
1563	PRO	CA	35.695	34.996	47.370	16.44
1564	PRO	C	35.343	33.936	48.410	16.53
1565	PRO	O	36.174	33.495	49.169	15.74
1566	PRO	CB	35.085	36.348	47.744	16.53
1567	PRO	CG	34.912	37.008	46.367	18.72
1568	PRO	CD	34.518	35.878	45.431	16.72
1569	ALA	N	34.112	33.456	48.396	16.66
1570	ALA	CA	33.729	32.357	49.341	16.12
1571	ALA	C	34.496	31.057	49.241	15.23
1572	ALA	O	34.901	30.462	50.211	15.53
1573	ALA	CB	32.226	31.970	49.232	15.29
1574	SER	N	34.701	30.625	48.006	15.32
1575	SER	CA	35.478	29.414	47.823	15.79
1576	SER	C	36.944	29.511	48.170	13.45
1577	SER	O	37.543	28.637	48.804	13.08
1578	SER	CB	35.222	28.779	46.447	17.95
1579	SER	OG	35.486	29.689	45.407	26.88
1580	PHE	N	37.464	30.720	47.831	13.85
1581	PHE	CA	38.864	31.032	48.219	12.76
1582	PHE	C	39.021	31.081	49.708	12.10
1583	PHE	O	39.917	30.465	50.247	14.79
1584	PHE	CB	39.297	32.409	47.672	14.01
1585	PHE	CG	40.660	32.843	48.229	12.89
1586	PHE	CD1	41.853	32.277	47.736	10.70
1587	PHE	CD2	40.701	33.811	49.277	15.33
1588	PHE	CE1	43.092	32.636	48.324	13.65
1589	PHE	CE2	41.935	34.193	49.864	13.88
1590	PHE	CZ	43.111	33.585	49.388	14.38
1591	LEU	N	38.112	31.849	50.367	13.17
1592	LEU	CA	38.075	32.020	51.857	11.98
1593	LEU	C	37.823	30.760	52.651	11.69
1594	LEU	O	38.520	30.483	53.608	10.86
1595	LEU	CB	37.066	33.104	52.284	11.49
1596	LEU	CG	37.504	34.528	51.922	9.71
1597	LEU	CD1	38.642	35.024	52.815	12.65
1598	LEU	CD2	36.326	35.472	51.928	12.34
1599	ASN	N	36.872	29.960	52.146	13.52
1600	ASN	CA	36.726	28.586	52.660	14.70

1601	ASN	C	38.019	27.745	52.629	13.68
1602	ASN	O	38.453	27.118	53.596	13.48
1603	ASN	CB	35.555	27.891	51.921	15.31
1604	ASN	CG	35.254	26.492	52.493	16.04
1605	ASN	OD1	34.760	26.270	53.576	17.67
1606	ASN	ND2	35.582	25.465	51.694	15.77
1607	PHE	N	38.701	27.785	51.452	12.27
1608	PHE	CA	39.997	27.082	51.440	11.60
1609	PHE	C	41.052	27.661	52.365	11.61
1610	PHE	O	41.697	26.908	53.084	13.15
1611	PHE	CB	40.490	27.042	49.979	11.94
1612	PHE	CG	41.868	26.456	49.776	11.78
1613	PHE	CD1	43.009	27.294	49.766	14.00
1614	PHE	CD2	42.033	25.070	49.586	11.64
1615	PHE	CE1	44.296	26.727	49.592	10.61
1616	PHE	CE2	43.329	24.515	49.407	12.07
1617	PHE	CZ	44.460	25.345	49.407	10.24
1618	LEU	N	41.208	29.021	52.358	10.72
1619	LEU	CA	42.131	29.689	53.281	10.36
1620	LEU	C	41.892	29.328	54.775	11.41
1621	LEU	O	42.776	29.036	55.575	8.72
1622	LEU	CB	42.039	31.214	53.107	9.30
1623	LEU	CG	42.908	32.004	54.144	11.24
1624	LEU	CD1	42.781	33.509	53.999	9.97
1625	LEU	CD2	44.376	31.595	54.123	8.08
1626	PHE	N	40.589	29.343	55.118	13.37
1627	PHE	CA	40.178	28.962	56.483	14.13
1628	PHE	C	40.391	27.509	56.789	14.10
1629	PHE	O	40.855	27.222	57.866	16.46
1630	PHE	CB	38.766	29.443	56.760	14.59
1631	PHE	CG	38.772	30.884	57.201	17.38
1632	PHE	CD1	39.357	31.890	56.414	17.66
1633	PHE	CD2	38.132	31.220	58.421	20.46
1634	PHE	CE1	39.363	33.222	56.859	17.85
1635	PHE	CE2	38.121	32.566	58.855	21.97
1636	PHE	CZ	38.761	33.551	58.091	19.00
1637	LYS	N	40.227	26.595	55.788	14.03
1638	LYS	CA	40.694	25.200	56.007	13.68
1639	LYS	C	42.139	25.064	56.362	13.76
1640	LYS	O	42.514	24.340	57.275	13.17
1641	LYS	CB	40.525	24.284	54.793	17.74
1642	LYS	CG	39.416	23.233	54.857	26.69
1643	LYS	CD	39.759	21.835	55.418	32.82
1644	LYS	CE	38.482	20.926	55.564	34.45
1645	LYS	NZ	38.794	19.520	55.920	39.18
1646	VAL	N	43.001	25.790	55.589	13.89

1647	VAL	CA	44.422	25.885	55.972	11.86
1648	VAL	C	44.678	26.442	57.355	11.86
1649	VAL	O	45.304	25.794	58.182	11.98
1650	VAL	CB	45.238	26.728	54.971	12.00
1651	VAL	CG1	44.967	26.260	53.509	11.88
1652	VAL	CG2	46.748	26.651	55.285	12.37
1653	ARG	N	44.126	27.628	57.609	12.93
1654	ARG	CA	44.218	28.196	58.973	14.48
1655	ARG	C	43.774	27.269	60.139	16.45
1656	ARG	O	44.486	27.063	61.113	17.22
1657	ARG	CB	43.366	29.447	59.011	13.76
1658	ARG	CG	44.037	30.657	58.430	12.22
1659	ARG	CD	43.028	31.823	58.494	13.67
1660	ARG	NE	43.712	33.077	58.134	15.68
1661	ARG	CZ	43.554	34.198	58.799	14.21
1662	ARG	NH1	42.626	34.342	59.706	12.91
1663	ARG	NH2	44.379	35.143	58.580	12.03
1664	GLU	N	42.622	26.635	59.960	16.23
1665	GLU	CA	42.097	25.723	60.976	16.92
1666	GLU	C	42.975	24.566	61.298	16.63
1667	GLU	O	43.037	24.051	62.388	17.05
1668	GLU	CB	40.849	25.081	60.476	21.77
1669	GLU	CG	39.696	26.051	60.316	30.11
1670	GLU	CD	38.885	26.144	61.587	37.62
1671	GLU	OE1	38.166	27.160	61.732	42.75
1672	GLU	OE2	38.978	25.220	62.436	39.25
1673	SER	N	43.731	24.148	60.295	16.50
1674	SER	CA	44.592	22.981	60.481	17.63
1675	SER	C	45.788	23.113	61.450	20.41
1676	SER	O	46.550	22.181	61.695	21.90
1677	SER	CB	45.172	22.503	59.108	14.84
1678	SER	OG	46.254	23.396	58.735	13.92
1679	GLY	N	46.011	24.359	61.919	20.72
1680	GLY	CA	47.237	24.604	62.671	20.75
1681	GLY	C	48.494	24.856	61.883	22.62
1682	GLY	O	49.516	25.236	62.431	25.75
1683	SER	N	48.416	24.672	60.541	20.77
1684	SER	CA	49.659	24.779	59.772	20.37
1685	SER	C	50.360	26.137	59.773	22.30
1686	SER	O	51.559	26.233	59.585	22.94
1687	SER	CB	49.485	24.400	58.287	17.21
1688	SER	OG	49.026	23.044	58.151	16.17
1689	LEU	N	49.548	27.204	59.963	22.44
1690	LEU	CA	50.024	28.615	59.942	25.58
1691	LEU	C	50.572	29.143	61.293	29.18
1692	LEU	O	50.849	30.302	61.553	34.54

1693	LEU	CB	48.951	29.616	59.439	23.62
1694	LEU	CG	48.548	29.235	58.027	22.66
1695	LEU	CD1	49.689	29.422	57.098	23.63
1696	LEU	CD2	47.444	30.047	57.437	25.59
1697	SER	N	50.649	28.205	62.203	27.88
1698	SER	CA	50.934	28.588	63.544	28.98
1699	SER	C	52.365	28.767	63.829	29.17
1700	SER	O	53.212	28.114	63.230	29.28
1701	SER	CB	50.428	27.503	64.367	29.56
1702	SER	OG	49.070	27.851	64.442	38.82
1703	PRO	N	52.649	29.669	64.766	28.99
1704	PRO	CA	54.068	29.983	64.955	28.15
1705	PRO	C	54.893	28.912	65.712	27.34
1706	PRO	O	56.103	28.986	65.759	28.43
1707	PRO	CB	53.940	31.338	65.624	29.14
1708	PRO	CG	52.734	31.150	66.539	28.91
1709	PRO	CD	51.769	30.350	65.692	28.77
1710	GLU	N	54.222	27.885	66.248	25.89
1711	GLU	CA	54.930	26.738	66.757	27.19
1712	GLU	C	55.561	25.818	65.688	26.00
1713	GLU	O	56.405	24.951	65.946	25.89
1714	GLU	CB	54.031	26.017	67.792	33.55
1715	GLU	CG	52.691	25.276	67.504	41.02
1716	GLU	CD	51.512	26.145	67.001	47.74
1717	GLU	OE1	51.521	27.382	67.117	49.25
1718	GLU	OE2	50.550	25.570	66.459	51.04
1719	HIS	N	55.110	26.077	64.437	21.92
1720	HIS	CA	55.663	25.415	63.239	18.96
1721	HIS	C	56.588	26.312	62.464	17.83
1722	HIS	O	56.466	27.528	62.564	17.07
1723	HIS	CB	54.545	25.023	62.270	20.94
1724	HIS	CG	53.668	24.065	63.047	20.70
1725	HIS	ND1	52.366	24.242	63.288	22.42
1726	HIS	CD2	54.077	22.872	63.652	19.89
1727	HIS	CE1	51.937	23.170	64.033	18.97
1728	HIS	NE2	52.998	22.336	64.244	19.93
1729	GLY	N	57.430	25.669	61.628	16.31
1730	GLY	CA	58.102	26.449	60.582	14.07
1731	GLY	C	57.110	27.069	59.607	12.35
1732	GLY	O	55.911	26.804	59.695	13.46
1733	PRO	N	57.602	27.933	58.693	11.56
1734	PRO	CA	56.641	28.612	57.833	13.06
1735	PRO	C	55.989	27.621	56.834	12.70
1736	PRO	O	56.633	26.687	56.321	13.68
1737	PRO	CB	57.455	29.724	57.210	11.82
1738	PRO	CG	58.892	29.277	57.324	12.42

1739	PRO	CD	58.963	28.340	58.496	11.92
1740	VAL	N	54.674	27.911	56.610	12.70
1741	VAL	CA	53.984	27.163	55.557	12.91
1742	VAL	C	54.744	27.391	54.248	13.19
1743	VAL	O	55.220	28.484	53.926	11.64
1744	VAL	CB	52.499	27.578	55.507	13.06
1745	VAL	CG1	51.592	26.621	54.745	14.25
1746	VAL	CG2	52.321	28.992	54.937	13.39
1747	VAL	N	54.874	26.281	53.520	12.59
1748	VAL	CA	55.295	26.380	52.106	11.98
1749	VAL	C	54.101	26.584	51.157	12.38
1750	VAL	O	53.183	25.771	51.097	15.24
1751	VAL	CB	56.061	25.107	51.706	9.51
1752	VAL	CG1	57.319	24.946	52.599	9.49
1753	VAL	CG2	56.454	25.144	50.213	10.06
1754	VAL	N	54.126	27.689	50.434	10.51
1755	VAL	CA	53.077	27.963	49.445	10.15
1756	VAL	C	53.712	27.938	48.046	11.07
1757	VAL	O	54.761	28.530	47.785	11.12
1758	VAL	CB	52.435	29.351	49.698	9.24
1759	VAL	CG1	51.958	29.592	51.143	8.57
1760	VAL	CG2	51.325	29.657	48.689	9.28
1761	HIS	N	53.032	27.235	47.133	10.38
1762	HIS	CA	53.504	27.236	45.747	8.48
1763	HIS	C	52.373	27.222	44.762	10.06
1764	HIS	O	51.254	26.782	45.047	9.96
1765	HIS	CB	54.558	26.153	45.458	8.91
1766	HIS	CG	53.991	24.769	45.162	8.64
1767	HIS	ND1	53.572	24.395	43.919	7.44
1768	HIS	CD2	53.803	23.723	46.048	8.51
1769	HIS	CE1	53.098	23.130	43.981	9.19
1770	HIS	NE2	53.243	22.739	45.290	11.46
1771	CYS	N	52.695	27.766	43.579	10.31
1772	CYS	CA	51.889	27.543	42.384	8.62
1773	CYS	C	52.821	26.996	41.318	9.41
1774	CYS	O	53.697	26.240	41.661	9.11
1775	CYS	CB	51.158	28.783	41.966	9.94
1776	CYS	SG	52.104	30.295	42.054	10.94
1777	SER	N	52.652	27.373	40.056	9.15
1778	SER	CA	53.690	26.848	39.157	8.78
1779	SER	C	55.026	27.639	39.274	8.55
1780	SER	O	56.127	27.100	39.390	8.15
1781	SER	CB	53.108	26.847	37.734	7.93
1782	SER	OG	54.103	26.437	36.830	8.26
1783	ALA	N	54.879	28.997	39.335	8.61
1784	ALA	CA	56.088	29.824	39.571	7.66

1785	ALA	C	56.362	30.302	41.022	8.82
1786	ALA	O	57.443	30.767	41.388	11.75
1787	ALA	CB	55.994	31.024	38.665	7.00
1788	GLY	N	55.332	30.135	41.872	8.66
1789	GLY	CA	55.504	30.616	43.255	8.32
1790	GLY	C	55.306	32.127	43.454	9.76
1791	GLY	O	55.810	32.695	44.413	10.12
1792	ILE	N	54.593	32.756	42.493	11.14
1793	ILE	CA	54.394	34.217	42.519	12.07
1794	ILE	C	52.948	34.722	42.312	10.76
1795	ILE	O	52.428	35.499	43.094	12.85
1796	ILE	CB	55.434	34.998	41.644	8.68
1797	ILE	CG1	55.274	34.717	40.134	9.17
1798	ILE	CG2	56.862	34.670	42.093	8.98
1799	ILE	CD1	56.328	35.365	39.216	7.46
1800	GLY	N	52.269	34.172	41.269	10.38
1801	GLY	CA	50.932	34.709	40.970	9.10
1802	GLY	C	49.783	34.383	41.944	10.90
1803	GLY	O	49.349	35.185	42.763	10.20
1804	ARG	N	49.366	33.089	41.810	11.01
1805	ARG	CA	48.418	32.462	42.759	10.63
1806	ARG	C	48.954	32.468	44.215	10.18
1807	ARG	O	48.254	32.844	45.134	10.97
1808	ARG	CB	48.025	31.034	42.275	9.12
1809	ARG	CG	47.247	31.120	40.967	9.78
1810	ARG	CD	47.007	29.785	40.293	7.58
1811	ARG	NE	48.188	29.323	39.636	8.89
1812	ARG	CZ	48.221	28.218	38.919	9.55
1813	ARG	NH1	47.173	27.474	38.805	10.16
1814	ARG	NH2	49.286	27.911	38.225	9.68
1815	SER	N	50.258	32.092	44.358	10.07
1816	SER	CA	50.854	32.120	45.724	8.26
1817	SER	C	50.864	33.513	46.362	10.19
1818	SER	O	50.529	33.638	47.522	10.34
1819	SER	CB	52.294	31.691	45.717	8.89
1820	SER	OG	52.445	30.336	45.240	11.05
1821	GLY	N	51.192	34.586	45.584	10.44
1822	GLY	CA	51.137	35.968	46.103	8.60
1823	GLY	C	49.743	36.409	46.483	9.62
1824	GLY	O	49.523	37.100	47.455	11.83
1825	THR	N	48.755	35.971	45.676	11.37
1826	THR	CA	47.324	36.271	45.940	10.02
1827	THR	C	46.841	35.647	47.237	11.10
1828	THR	O	46.328	36.337	48.121	9.82
1829	THR	CB	46.392	35.796	44.796	9.53
1830	THR	OG1	46.832	36.337	43.530	10.14

1831	THR	CG2	44.927	36.128	45.095	8.73
1832	PHE	N	47.096	34.326	47.377	9.10
1833	PHE	CA	46.838	33.635	48.636	10.60
1834	PHE	C	47.384	34.332	49.931	10.58
1835	PHE	O	46.702	34.625	50.911	11.24
1836	PHE	CB	47.311	32.168	48.478	8.88
1837	PHE	CG	47.118	31.324	49.741	9.58
1838	PHE	CD1	45.907	30.608	49.935	11.54
1839	PHE	CD2	48.151	31.261	50.713	11.23
1840	PHE	CE1	45.741	29.809	51.090	6.44
1841	PHE	CE2	47.985	30.464	51.879	9.94
1842	PHE	CZ	46.787	29.741	52.023	6.47
1843	CYS	N	48.703	34.583	49.832	10.70
1844	CYS	CA	49.413	35.190	50.962	10.02
1845	CYS	C	49.027	36.625	51.272	10.89
1846	CYS	O	48.945	37.006	52.423	12.32
1847	CYS	CB	50.929	35.091	50.816	12.17
1848	CYS	SG	51.574	33.397	50.718	15.41
1849	LEU	N	48.766	37.424	50.215	10.01
1850	LEU	CA	48.287	38.785	50.451	10.37
1851	LEU	C	46.994	38.815	51.257	10.12
1852	LEU	O	46.890	39.510	52.246	9.30
1853	LEU	CB	48.149	39.524	49.125	9.12
1854	LEU	CG	47.758	40.996	49.225	11.23
1855	LEU	CD1	47.427	41.612	47.834	11.32
1856	LEU	CD2	48.778	41.823	50.020	11.96
1857	ALA	N	46.015	37.982	50.789	10.91
1858	ALA	CA	44.724	37.906	51.492	10.80
1859	ALA	C	44.906	37.426	52.955	11.33
1860	ALA	O	44.454	38.026	53.923	10.76
1861	ALA	CB	43.764	36.998	50.732	7.83
1862	ASP	N	45.678	36.373	53.117	11.75
1863	ASP	CA	45.996	35.908	54.497	11.91
1864	ASP	C	46.600	36.952	55.469	11.55
1865	ASP	O	46.156	37.208	56.590	11.95
1866	ASP	CB	46.840	34.628	54.482	10.16
1867	ASP	CG	46.956	34.094	55.912	13.48
1868	ASP	OD1	45.954	33.856	56.609	12.31
1869	ASP	OD2	48.073	33.934	56.360	12.63
1870	THR	N	47.625	37.598	54.924	10.97
1871	THR	CA	48.347	38.561	55.751	11.02
1872	THR	C	47.504	39.800	55.982	11.79
1873	THR	O	47.502	40.323	57.088	11.99
1874	THR	CB	49.692	39.040	55.137	11.07
1875	THR	OG1	50.625	37.985	55.158	11.80
1876	THR	CG2	50.336	40.218	55.881	10.36

1877	CYS	N	46.764	40.247	54.943	10.65
1878	CYS	CA	45.827	41.365	55.230	10.63
1879	CYS	C	44.740	41.106	56.320	12.96
1880	CYS	O	44.486	41.919	57.205	13.56
1881	CYS	CB	45.123	41.924	53.999	10.48
1882	CYS	SG	46.329	42.755	52.937	13.42
1883	LEU	N	44.189	39.878	56.268	10.64
1884	LEU	CA	43.255	39.449	57.316	11.23
1885	LEU	C	43.865	39.322	58.731	12.65
1886	LEU	O	43.280	39.757	59.707	14.44
1887	LEU	CB	42.560	38.133	56.873	9.49
1888	LEU	CG	41.665	38.328	55.653	8.57
1889	LEU	CD1	40.477	39.186	55.978	10.68
1890	LEU	CD2	41.173	37.002	55.114	11.48
1891	LEU	N	45.089	38.753	58.780	13.24
1892	LEU	CA	45.873	38.751	60.039	12.90
1893	LEU	C	46.154	40.116	60.664	13.36
1894	LEU	O	45.961	40.401	61.827	15.00
1895	LEU	CB	47.209	38.118	59.742	12.90
1896	LEU	CG	47.717	37.083	60.724	17.31
1897	LEU	CD1	47.104	37.072	62.115	17.90
1898	LEU	CD2	49.240	37.021	60.648	17.91
1899	LEU	N	46.613	41.024	59.811	14.06
1900	LEU	CA	46.725	42.436	60.177	15.83
1901	LEU	C	45.461	43.107	60.760	15.86
1902	LEU	O	45.460	43.682	61.849	15.48
1903	LEU	CB	47.201	43.234	58.964	15.91
1904	LEU	CG	48.624	43.774	58.904	18.29
1905	LEU	CD1	49.052	43.573	57.469	20.36
1906	LEU	CD2	49.641	43.305	59.923	16.23
1907	MET	N	44.375	42.978	59.989	14.06
1908	MET	CA	43.106	43.427	60.510	16.10
1909	MET	C	42.674	42.850	61.894	18.37
1910	MET	O	42.126	43.531	62.759	17.82
1911	MET	CB	42.118	43.137	59.401	17.90
1912	MET	CG	40.713	43.550	59.741	22.88
1913	MET	SD	39.601	43.214	58.369	27.93
1914	MET	CE	40.671	43.783	57.014	21.01
1915	ASP	N	42.996	41.548	62.049	17.66
1916	ASP	CA	42.752	40.766	63.290	18.72
1917	ASP	C	43.468	41.301	64.551	20.72
1918	ASP	O	42.988	41.449	65.670	18.46
1919	ASP	CB	43.151	39.310	62.959	15.77
1920	ASP	CG	42.280	38.294	63.654	15.78
1921	ASP	OD1	41.335	38.723	64.270	15.30
1922	ASP	OD2	42.563	37.090	63.595	12.03

1923	LYS	N	44.725	41.679	64.309	22.67
1924	LYS	CA	45.442	42.083	65.515	26.79
1925	LYS	C	45.030	43.365	66.118	27.91
1926	LYS	O	45.173	43.640	67.292	27.25
1927	LYS	CB	46.939	42.117	65.368	31.63
1928	LYS	CG	47.623	43.011	64.367	36.21
1929	LYS	CD	49.088	42.561	64.344	41.15
1930	LYS	CE	49.122	41.080	63.907	45.83
1931	LYS	NZ	49.950	40.195	64.789	48.52
1932	ARG	N	44.496	44.183	65.244	29.18
1933	ARG	CA	44.107	45.458	65.814	30.25
1934	ARG	C	42.610	45.701	65.816	28.51
1935	ARG	O	42.101	46.694	66.298	29.83
1936	ARG	CB	44.909	46.490	65.022	35.96
1937	ARG	CG	44.730	46.304	63.509	35.60
1938	ARG	CD	45.670	47.261	62.794	39.72
1939	ARG	NE	47.048	46.827	62.880	44.72
1940	ARG	CZ	47.922	47.107	61.918	49.49
1941	ARG	NH1	47.618	47.655	60.744	46.55
1942	ARG	NH2	49.174	46.847	62.219	54.27
1943	LYS	N	41.920	44.731	65.188	24.03
1944	LYS	CA	40.522	44.893	64.863	22.66
1945	LYS	C	40.206	46.220	64.139	22.19
1946	LYS	O	39.223	46.916	64.337	22.54
1947	LYS	CB	39.649	44.455	66.104	23.45
1948	LYS	CG	39.743	42.957	66.570	20.10
1949	LYS	CD	39.208	41.813	65.634	20.71
1950	LYS	CE	39.159	40.316	66.166	17.94
1951	LYS	NZ	38.787	39.163	65.278	27.72
1952	ASP	N	41.140	46.551	63.222	21.48
1953	ASP	CA	41.082	47.870	62.548	22.85
1954	ASP	C	41.316	47.877	61.015	21.41
1955	ASP	O	42.375	48.119	60.444	21.48
1956	ASP	CB	41.986	48.893	63.285	25.58
1957	ASP	CG	41.991	50.280	62.654	29.64
1958	ASP	OD1	41.113	50.584	61.818	31.77
1959	ASP	OD2	42.919	51.024	62.980	30.41
1960	PRO	N	40.247	47.578	60.311	20.58
1961	PRO	CA	40.371	47.322	58.886	22.04
1962	PRO	C	40.829	48.515	58.129	24.22
1963	PRO	O	41.512	48.463	57.118	22.77
1964	PRO	CB	38.944	47.032	58.454	23.82
1965	PRO	CG	38.145	46.699	59.709	22.76
1966	PRO	CD	38.893	47.416	60.819	22.17
1967	SER	N	40.411	49.657	58.676	26.49
1968	SER	CA	40.771	50.891	57.983	29.21

1969	SER	C	42.244	51.221	58.015	28.16
1970	SER	O	42.769	51.948	57.184	30.98
1971	SER	CB	39.918	52.100	58.446	32.36
1972	SER	OG	38.686	52.172	57.658	37.57
1973	SER	N	42.922	50.561	58.956	25.94
1974	SER	CA	44.384	50.605	58.947	23.97
1975	SER	C	45.142	49.677	58.018	23.07
1976	SER	O	46.361	49.640	58.035	23.41
1977	SER	CB	44.987	50.283	60.317	24.53
1978	SER	OG	44.902	48.866	60.519	26.18
1979	VAL	N	44.421	48.864	57.246	22.45
1980	VAL	CA	45.137	48.031	56.270	21.20
1981	VAL	C	45.123	48.557	54.850	21.26
1982	VAL	O	44.092	48.802	54.231	22.49
1983	VAL	CB	45.002	46.493	56.466	22.58
1984	VAL	CG1	44.884	45.658	55.190	20.76
1985	VAL	CG2	44.174	46.080	57.682	17.17
1986	ASP	N	46.355	48.833	54.405	19.92
1987	ASP	CA	46.605	49.285	53.043	19.98
1988	ASP	C	47.081	48.123	52.164	17.61
1989	ASP	O	48.232	47.702	52.203	18.51
1990	ASP	CB	47.639	50.404	53.178	21.39
1991	ASP	CG	47.956	51.130	51.885	25.31
1992	ASP	OD1	47.820	50.542	50.821	23.58
1993	ASP	OD2	48.409	52.287	51.944	32.08
1994	ILE	N	46.134	47.556	51.413	18.00
1995	ILE	CA	46.483	46.335	50.680	16.17
1996	ILE	C	47.626	46.519	49.725	16.20
1997	ILE	O	48.485	45.657	49.701	16.71
1998	ILE	CB	45.244	45.758	49.959	18.69
1999	ILE	CG1	44.185	45.428	51.013	20.07
2000	ILE	CG2	45.559	44.493	49.137	16.13
2001	ILE	CD1	42.889	44.877	50.407	22.35
2002	LYS	N	47.646	47.644	48.951	15.61
2003	LYS	CA	48.796	47.807	48.039	16.12
2004	LYS	C	50.135	47.931	48.716	15.62
2005	LYS	O	51.153	47.394	48.321	15.12
2006	LYS	CB	48.689	49.055	47.235	18.84
2007	LYS	CG	47.447	49.010	46.334	31.31
2008	LYS	CD	47.091	50.385	45.684	37.73
2009	LYS	CE	47.284	51.463	46.766	43.40
2010	LYS	NZ	46.243	52.480	46.893	47.06
2011	LYS	N	50.099	48.648	49.820	16.19
2012	LYS	CA	51.282	48.662	50.657	17.17
2013	LYS	C	51.745	47.323	51.261	15.81
2014	LYS	O	52.929	47.020	51.262	13.38

2015	LYS	CB	51.004	49.698	51.724	21.47
2016	LYS	CG	52.262	50.268	52.260	26.41
2017	LYS	CD	52.080	51.628	52.944	32.75
2018	LYS	CE	51.717	52.861	52.072	37.01
2019	LYS	NZ	52.068	54.091	52.860	41.44
2020	VAL	N	50.779	46.493	51.746	15.38
2021	VAL	CA	51.243	45.153	52.147	13.40
2022	VAL	C	51.721	44.256	51.029	12.42
2023	VAL	O	52.682	43.538	51.174	12.19
2024	VAL	CB	50.424	44.394	53.259	17.62
2025	VAL	CG1	50.125	42.920	53.057	13.70
2026	VAL	CG2	49.369	45.253	53.949	14.26
2027	LEU	N	51.133	44.416	49.870	11.53
2028	LEU	CA	51.731	43.742	48.691	12.42
2029	LEU	C	53.154	44.176	48.316	11.91
2030	LEU	O	54.046	43.392	48.055	10.65
2031	LEU	CB	50.805	43.927	47.497	12.94
2032	LEU	CG	51.267	43.151	46.270	14.51
2033	LEU	CD1	50.310	43.372	45.083	14.86
2034	LEU	CD2	51.468	41.649	46.603	12.64
2035	LEU	N	53.356	45.507	48.366	14.10
2036	LEU	CA	54.728	46.026	48.214	13.57
2037	LEU	C	55.705	45.555	49.289	11.98
2038	LEU	O	56.801	45.159	48.950	10.15
2039	LEU	CB	54.659	47.567	48.096	15.92
2040	LEU	CG	54.751	48.229	46.702	18.96
2041	LEU	CD1	53.794	49.403	46.600	18.76
2042	LEU	CD2	54.861	47.323	45.482	20.15
2043	ASP	N	55.280	45.511	50.587	13.06
2044	ASP	CA	56.110	44.828	51.584	12.70
2045	ASP	C	56.460	43.385	51.230	11.44
2046	ASP	O	57.602	42.960	51.239	11.16
2047	ASP	CB	55.726	44.946	53.135	15.05
2048	ASP	CG	57.045	45.344	53.997	23.08
2049	ASP	OD1	57.469	46.507	54.030	22.88
2050	ASP	OD2	57.754	44.542	54.624	24.92
2051	MET	N	55.430	42.623	50.818	13.08
2052	MET	CA	55.755	41.284	50.344	12.59
2053	MET	C	56.726	41.161	49.161	10.76
2054	MET	O	57.544	40.258	49.155	9.86
2055	MET	CB	54.494	40.507	49.955	14.18
2056	MET	CG	53.772	39.803	51.043	20.95
2057	MET	SD	52.297	39.007	50.399	25.25
2058	MET	CE	51.819	38.502	52.033	24.15
2059	ARG	N	56.616	42.061	48.195	11.81
2060	ARG	CA	57.544	42.017	47.025	14.09

2061	ARG	C	59.018	42.435	47.298	14.19
2062	ARG	O	59.958	42.214	46.558	15.37
2063	ARG	CB	57.006	42.765	45.786	15.27
2064	ARG	CG	55.506	42.740	45.458	20.41
2065	ARG	CD	54.800	42.082	44.276	22.57
2066	ARG	NE	55.067	42.731	43.066	21.00
2067	ARG	CZ	54.603	42.591	41.803	19.36
2068	ARG	NH1	53.481	42.040	41.379	17.30
2069	ARG	NH2	55.419	43.076	40.926	15.47
2070	LYS	N	59.216	42.912	48.567	12.82
2071	LYS	CA	60.619	42.962	49.027	11.88
2072	LYS	C	61.320	41.630	49.166	11.52
2073	LYS	O	62.519	41.494	49.116	12.87
2074	LYS	CB	60.733	43.761	50.344	10.90
2075	LYS	CG	60.143	45.169	50.220	10.61
2076	LYS	CD	60.078	45.786	51.630	16.89
2077	LYS	CE	59.704	47.286	51.748	18.25
2078	LYS	NZ	59.840	47.665	53.175	18.64
2079	PHE	N	60.530	40.573	49.403	11.46
2080	PHE	CA	61.062	39.240	49.651	10.66
2081	PHE	C	60.961	38.264	48.481	10.63
2082	PHE	O	61.718	37.304	48.372	11.08
2083	PHE	CB	60.312	38.582	50.824	10.87
2084	PHE	CG	60.347	39.458	52.036	10.74
2085	PHE	CD1	61.470	39.374	52.899	14.67
2086	PHE	CD2	59.277	40.336	52.321	13.16
2087	PHE	CE1	61.505	40.174	54.080	14.61
2088	PHE	CE2	59.312	41.139	53.481	11.84
2089	PHE	CZ	60.439	41.068	54.334	12.78
2090	ARG	N	59.991	38.503	47.589	11.78
2091	ARG	CA	60.048	37.752	46.323	11.12
2092	ARG	C	59.438	38.615	45.199	10.70
2093	ARG	O	58.427	39.277	45.416	11.00
2094	ARG	CB	59.361	36.360	46.491	9.05
2095	ARG	CG	59.547	35.389	45.310	8.54
2096	ARG	CD	58.829	34.077	45.618	8.35
2097	ARG	NE	58.807	33.096	44.485	8.45
2098	ARG	CZ	59.812	32.305	44.135	8.44
2099	ARG	NH1	60.967	32.419	44.711	8.74
2100	ARG	NH2	59.670	31.395	43.187	9.54
2101	MET	N	60.064	38.542	43.986	11.10
2102	MET	CA	59.514	39.256	42.833	10.52
2103	MET	C	58.123	38.755	42.342	12.21
2104	MET	O	57.716	37.596	42.401	11.69
2105	MET	CB	60.515	39.157	41.664	12.40
2106	MET	CG	60.688	37.693	41.161	13.12

2107	MET	SD	61.708	37.587	39.673	12.49
2108	MET	CE	63.258	38.266	40.330	14.52
2109	GLY	N	57.384	39.697	41.822	11.82
2110	GLY	CA	56.244	39.387	40.947	10.69
2111	GLY	C	55.014	38.778	41.578	11.80
2112	GLY	O	54.118	38.340	40.868	11.81
2113	LEU	N	54.995	38.855	42.924	11.43
2114	LEU	CA	53.802	38.497	43.681	11.39
2115	LEU	C	52.518	39.174	43.279	12.20
2116	LEU	O	52.384	40.390	43.261	12.24
2117	LEU	CB	54.050	38.674	45.197	10.83
2118	LEU	CG	55.281	37.955	45.738	9.47
2119	LEU	CD1	55.323	36.465	45.320	9.16
2120	LEU	CD2	55.336	38.148	47.254	10.38
2121	ILE	N	51.588	38.296	42.897	10.54
2122	ILE	CA	50.396	38.717	42.153	11.17
2123	ILE	C	50.699	39.082	40.678	13.75
2124	ILE	O	51.436	40.016	40.396	13.91
2125	ILE	CB	49.557	39.790	42.868	11.11
2126	ILE	CG1	49.177	39.212	44.233	9.13
2127	ILE	CG2	48.312	40.138	42.008	14.38
2128	ILE	CD1	48.073	39.967	44.918	8.65
2129	GLN	N	50.157	38.291	39.721	13.18
2130	GLN	CA	50.662	38.385	38.342	12.31
2131	GLN	C	49.766	39.112	37.360	14.51
2132	GLN	O	50.188	39.490	36.276	14.93
2133	GLN	CB	51.037	36.985	37.828	12.10
2134	GLN	CG	52.401	36.558	38.336	13.08
2135	GLN	CD	53.427	37.182	37.460	14.33
2136	GLN	OE1	53.477	36.854	36.292	16.45
2137	GLN	NE2	54.248	38.058	38.029	11.97
2138	THR	N	48.519	39.356	37.823	14.47
2139	THR	CA	47.567	40.130	37.057	13.82
2140	THR	C	46.787	41.158	37.866	15.31
2141	THR	O	46.656	41.081	39.092	15.21
2142	THR	CB	46.554	39.229	36.350	12.44
2143	THR	OG1	45.588	38.765	37.287	13.84
2144	THR	CG2	47.152	38.042	35.581	12.80
2145	ALA	N	46.231	42.152	37.125	16.12
2146	ALA	CA	45.346	43.159	37.762	17.15
2147	ALA	C	44.035	42.573	38.343	17.06
2148	ALA	O	43.495	43.018	39.351	16.84
2149	ALA	CB	44.987	44.299	36.780	15.40
2150	ASP	N	43.567	41.485	37.685	16.67
2151	ASP	CA	42.388	40.777	38.209	16.05
2152	ASP	C	42.651	39.978	39.460	14.16

2153	ASP	O	41.818	39.960	40.360	13.25
2154	ASP	CB	41.797	39.833	37.180	16.36
2155	ASP	CG	40.336	39.658	37.485	18.91
2156	ASP	OD1	39.640	40.638	37.769	19.27
2157	ASP	OD2	39.876	38.522	37.453	19.47
2158	GLN	N	43.857	39.397	39.542	12.74
2159	GLN	CA	44.257	38.815	40.853	12.47
2160	GLN	C	44.351	39.857	41.984	13.42
2161	GLN	O	43.906	39.646	43.101	13.68
2162	GLN	CB	45.579	38.040	40.754	10.94
2163	GLN	CG	45.467	36.777	39.876	10.93
2164	GLN	CD	46.795	36.101	39.634	11.89
2165	GLN	OE1	47.863	36.660	39.815	13.27
2166	GLN	NE2	46.739	34.859	39.129	10.17
2167	LEU	N	44.892	41.066	41.654	15.21
2168	LEU	CA	44.818	42.209	42.611	13.64
2169	LEU	C	43.408	42.567	43.025	14.41
2170	LEU	O	43.078	42.676	44.201	15.65
2171	LEU	CB	45.560	43.441	42.074	12.86
2172	LEU	CG	45.681	44.598	43.045	13.02
2173	LEU	CD1	46.174	45.889	42.389	12.87
2174	LEU	CD2	46.540	44.205	44.235	12.32
2175	ARG	N	42.543	42.691	41.995	13.43
2176	ARG	CA	41.161	42.989	42.303	13.38
2177	ARG	C	40.433	41.964	43.135	14.16
2178	ARG	O	39.716	42.292	44.066	14.64
2179	ARG	CB	40.407	43.216	41.022	13.46
2180	ARG	CG	38.925	43.525	41.286	13.29
2181	ARG	CD	38.171	43.714	39.976	16.52
2182	ARG	NE	36.823	44.228	40.247	20.17
2183	ARG	CZ	35.772	43.485	40.354	19.49
2184	ARG	NH1	35.807	42.186	40.332	20.88
2185	ARG	NH2	34.650	44.103	40.484	21.32
2186	PHE	N	40.683	40.692	42.778	13.41
2187	PHE	CA	40.279	39.551	43.612	13.00
2188	PHE	C	40.781	39.564	45.054	12.42
2189	PHE	O	40.006	39.259	45.937	14.84
2190	PHE	CB	40.652	38.200	42.969	12.87
2191	PHE	CG	40.024	37.029	43.724	13.08
2192	PHE	CD1	38.719	36.588	43.410	15.82
2193	PHE	CD2	40.732	36.435	44.792	13.48
2194	PHE	CE1	38.069	35.621	44.224	14.88
2195	PHE	CE2	40.074	35.497	45.610	14.71
2196	PHE	CZ	38.737	35.123	45.347	13.48
2197	SER	N	42.069	39.939	45.279	12.86
2198	SER	CA	42.661	40.146	46.627	13.82

2199	SER	C	41.892	41.095	47.511	15.06
2200	SER	O	41.566	40.755	48.633	15.36
2201	SER	CB	44.037	40.790	46.596	11.50
2202	SER	OG	44.867	39.808	46.005	19.07
2203	TYR	N	41.541	42.275	46.959	14.37
2204	TYR	CA	40.568	43.166	47.642	13.98
2205	TYR	C	39.191	42.565	47.958	14.72
2206	TYR	O	38.720	42.678	49.061	16.92
2207	TYR	CB	40.237	44.390	46.809	15.56
2208	TYR	CG	41.257	45.499	46.833	15.10
2209	TYR	CD1	42.504	45.344	46.171	15.01
2210	TYR	CD2	40.898	46.710	47.477	16.69
2211	TYR	CE1	43.433	46.405	46.232	17.26
2212	TYR	CE2	41.786	47.793	47.473	17.79
2213	TYR	CZ	43.052	47.618	46.872	18.91
2214	TYR	OH	43.970	48.651	46.941	22.03
2215	LEU	N	38.561	41.892	46.996	14.60
2216	LEU	CA	37.297	41.190	47.263	13.80
2217	LEU	C	37.350	40.153	48.419	13.84
2218	LEU	O	36.585	40.029	49.351	15.22
2219	LEU	CB	36.998	40.456	45.966	15.22
2220	LEU	CG	35.889	40.943	45.032	17.91
2221	LEU	CD1	36.181	40.536	43.608	17.36
2222	LEU	CD2	35.469	42.386	45.200	17.38
2223	ALA	N	38.419	39.344	48.343	13.18
2224	ALA	CA	38.629	38.360	49.433	12.65
2225	ALA	C	38.897	38.956	50.826	14.16
2226	ALA	O	38.371	38.463	51.807	14.00
2227	ALA	CB	39.768	37.370	49.099	13.02
2228	VAL	N	39.721	40.035	50.884	11.78
2229	VAL	CA	39.918	40.769	52.138	12.53
2230	VAL	C	38.651	41.510	52.651	13.82
2231	VAL	O	38.291	41.427	53.828	12.86
2232	VAL	CB	41.111	41.728	52.070	11.66
2233	VAL	CG1	42.380	40.915	51.747	13.24
2234	VAL	CG2	41.316	42.491	53.376	9.92
2235	ILE	N	37.962	42.204	51.727	12.29
2236	ILE	CA	36.692	42.836	52.151	13.94
2237	ILE	C	35.643	41.821	52.683	14.15
2238	ILE	O	35.051	42.017	53.733	14.06
2239	ILE	CB	36.150	43.725	50.998	13.50
2240	ILE	CG1	37.132	44.878	50.705	14.91
2241	ILE	CG2	34.736	44.246	51.344	12.74
2242	ILE	CD1	36.837	45.561	49.370	13.99
2243	GLU	N	35.524	40.682	51.982	13.27
2244	GLU	CA	34.623	39.640	52.511	12.79

2245	GLU	C	35.054	38.960	53.810	14.22
2246	GLU	O	34.348	38.838	54.812	14.98
2247	GLU	CB	34.469	38.619	51.428	11.88
2248	GLU	CG	33.577	37.436	51.758	12.69
2249	GLU	CD	32.144	37.802	52.097	18.61
2250	GLU	OE1	31.662	38.871	51.750	19.68
2251	GLU	OE2	31.437	37.016	52.719	20.07
2252	GLY	N	36.351	38.579	53.807	14.10
2253	GLY	CA	36.996	38.012	55.024	11.35
2254	GLY	C	36.903	38.905	56.279	12.42
2255	GLY	O	36.792	38.436	57.408	14.09
2256	ALA	N	36.936	40.244	56.035	12.11
2257	ALA	CA	36.786	41.194	57.129	13.24
2258	ALA	C	35.555	40.936	57.966	14.50
2259	ALA	O	35.567	41.104	59.163	15.74
2260	ALA	CB	36.717	42.628	56.649	12.85
2261	LYS	N	34.522	40.415	57.318	15.43
2262	LYS	CA	33.316	40.077	58.087	17.97
2263	LYS	C	33.511	39.126	59.305	18.17
2264	LYS	O	33.007	39.309	60.412	16.72
2265	LYS	CB	32.232	39.479	57.184	17.36
2266	LYS	CG	31.843	40.457	56.080	20.89
2267	LYS	CD	30.798	39.777	55.206	19.35
2268	LYS	CE	30.249	40.618	54.078	21.45
2269	LYS	NZ	29.750	39.613	53.147	28.58
2270	PHE	N	34.298	38.096	58.987	17.06
2271	PHE	CA	34.710	37.136	60.018	17.26
2272	PHE	C	35.681	37.783	61.042	17.65
2273	PHE	O	35.418	37.750	62.227	17.35
2274	PHE	CB	35.243	35.871	59.313	16.04
2275	PHE	CG	35.710	34.853	60.327	18.17
2276	PHE	CD1	36.999	34.982	60.906	18.77
2277	PHE	CD2	34.842	33.806	60.681	17.46
2278	PHE	CE1	37.423	34.059	61.897	18.56
2279	PHE	CE2	35.280	32.867	61.642	17.26
2280	PHE	CZ	36.551	33.006	62.234	16.76
2281	ILE	N	36.741	38.443	60.524	17.16
2282	ILE	CA	37.667	39.052	61.474	16.95
2283	ILE	C	36.960	40.030	62.419	18.22
2284	ILE	O	37.307	40.294	63.547	19.58
2285	ILE	CB	38.752	39.831	60.687	16.65
2286	ILE	CG1	39.499	39.025	59.668	15.20
2287	ILE	CG2	39.745	40.510	61.608	17.33

2288	ILE	CD1	40.138	37.768	60.180	16.00
2289	MET	N	35.924	40.676	61.869	17.76
2290	MET	CA	35.293	41.696	62.708	17.15
2291	MET	C	34.125	41.213	63.554	18.59
2292	MET	O	33.271	42.006	63.936	18.92
2293	MET	CB	34.850	42.902	61.856	18.33
2294	MET	CG	36.096	43.579	61.237	18.10
2295	MET	SD	37.293	44.167	62.479	22.98
2296	MET	CE	36.332	45.615	62.928	22.14
2297	GLY	N	34.097	39.878	63.787	17.81
2298	GLY	CA	33.117	39.341	64.764	19.24
2299	GLY	C	31.932	38.467	64.303	18.12
2300	GLY	O	31.162	37.852	65.052	18.31
2301	ASP	N	31.751	38.493	62.977	16.53
2302	ASP	CA	30.662	37.671	62.462	17.00
2303	ASP	C	31.116	36.272	62.108	18.13
2304	ASP	O	31.346	35.891	60.957	19.06
2305	ASP	CB	29.981	38.377	61.275	18.82
2306	ASP	CG	28.755	37.606	60.749	20.22
2307	ASP	OD1	28.315	36.651	61.382	19.51
2308	ASP	OD2	28.234	37.955	59.688	23.56
2309	SER	N	31.276	35.460	63.182	18.73
2310	SER	CA	31.804	34.126	62.883	16.96
2311	SER	C	30.962	33.233	61.948	18.39
2312	SER	O	31.432	32.300	61.284	18.33
2313	SER	CB	32.076	33.353	64.164	17.13
2314	SER	OG	33.211	33.889	64.866	14.25
2315	SER	N	29.647	33.584	61.904	17.50
2316	SER	CA	28.726	32.804	61.055	18.74
2317	SER	C	28.994	32.849	59.528	17.75
2318	SER	O	28.665	31.927	58.776	16.68
2319	SER	CB	27.259	33.169	61.335	19.67
2320	SER	OG	26.885	34.432	60.758	21.88
2321	VAL	N	29.690	33.918	59.107	17.27
2322	VAL	CA	30.098	33.858	57.707	18.22
2323	VAL	C	30.893	32.658	57.299	18.73
2324	VAL	O	30.749	32.254	56.163	19.63
2325	VAL	CB	30.851	35.081	57.155	20.69
2326	VAL	CG1	32.145	35.419	57.906	17.79
2327	VAL	CG2	29.886	36.225	56.907	23.70
2328	GLN	N	31.676	32.100	58.244	18.28
2329	GLN	CA	32.498	30.973	57.851	19.78
2330	GLN	C	31.709	29.809	57.296	23.25
2331	GLN	O	31.866	29.325	56.194	25.12
2332	GLN	CB	33.356	30.549	59.027	20.56
2333	GLN	CG	34.279	29.396	58.650	24.84

2334	GLN	CD	35.223	29.031	59.768	27.26
2335	GLN	OE1	35.456	29.725	60.745	31.04
2336	GLN	NE2	35.798	27.883	59.602	29.42
2337	ASP	N	30.649	29.485	58.075	25.31
2338	ASP	CA	29.810	28.447	57.454	27.02
2339	ASP	C	28.987	28.769	56.202	25.79
2340	ASP	O	28.680	27.943	55.345	25.32
2341	ASP	CB	29.058	27.677	58.540	35.78
2342	ASP	CG	30.060	26.695	59.218	44.92
2343	ASP	OD1	30.644	25.807	58.529	50.04
2344	ASP	OD2	30.268	26.816	60.445	50.59
2345	GLN	N	28.684	30.074	56.081	23.38
2346	GLN	CA	28.196	30.539	54.780	24.32
2347	GLN	C	29.105	30.389	53.573	23.16
2348	GLN	O	28.683	29.998	52.488	21.27
2349	GLN	CB	27.869	31.970	54.845	28.00
2350	GLN	CG	26.784	32.237	55.878	35.72
2351	GLN	CD	26.555	33.724	55.747	43.13
2352	GLN	OE1	26.549	34.281	54.641	48.57
2353	GLN	NE2	26.403	34.395	56.909	43.82
2354	TRP	N	30.382	30.678	53.819	20.29
2355	TRP	CA	31.346	30.362	52.750	19.31
2356	TRP	C	31.466	28.909	52.431	19.07
2357	TRP	O	31.450	28.527	51.271	19.20
2358	TRP	CB	32.784	30.779	53.114	19.26
2359	TRP	CG	32.909	32.243	53.480	15.65
2360	TRP	CD1	32.161	33.289	52.953	14.94
2361	TRP	CD2	33.865	32.827	54.394	15.85
2362	TRP	NE1	32.572	34.480	53.472	15.54
2363	TRP	CE2	33.623	34.245	54.377	15.86
2364	TRP	CE3	34.912	32.297	55.183	14.86
2365	TRP	CZ2	34.420	35.102	55.179	16.78
2366	TRP	CZ3	35.699	33.183	55.951	14.37
2367	TRP	CH2	35.460	34.572	55.969	15.56
2368	LYS	N	31.535	28.079	53.466	21.19
2369	LYS	CA	31.490	26.660	53.154	24.17
2370	LYS	C	30.299	26.154	52.302	25.28
2371	LYS	O	30.419	25.380	51.350	26.15
2372	LYS	CB	31.535	25.905	54.461	26.43
2373	LYS	CG	31.670	24.409	54.259	32.00
2374	LYS	CD	31.629	23.919	55.676	38.87
2375	LYS	CE	31.917	22.442	55.805	45.47
2376	LYS	NZ	31.660	22.084	57.228	51.74
2377	GLU	N	29.117	26.663	52.680	26.22
2378	GLU	CA	27.928	26.358	51.891	27.87
2379	GLU	C	27.975	26.877	50.455	26.53

2380	GLU	O	27.835	26.148	49.496	30.42
2381	GLU	CB	26.659	26.888	52.548	34.80
2382	GLU	CG	26.313	26.343	53.949	47.61
2383	GLU	CD	25.599	24.966	53.934	55.88
2384	GLU	OE1	24.348	24.925	53.838	59.76
2385	GLU	OE2	26.294	23.937	54.064	61.03
2386	LEU	N	28.258	28.163	50.302	24.19
2387	LEU	CA	28.499	28.736	48.972	23.43
2388	LEU	C	29.566	28.108	48.071	24.08
2389	LEU	O	29.553	28.130	46.848	22.85
2390	LEU	CB	29.014	30.112	49.163	25.02
2391	LEU	CG	27.980	31.163	49.085	25.39
2392	LEU	CD1	28.441	32.350	49.899	27.03
2393	LEU	CD2	26.614	30.675	49.478	28.40
2394	SER	N	30.563	27.564	48.762	23.22
2395	SER	CA	31.652	26.937	48.040	24.53
2396	SER	C	31.401	25.574	47.438	26.87
2397	SER	O	32.174	25.053	46.642	26.47
2398	SER	CB	32.858	26.864	48.941	23.92
2399	SER	OG	32.879	25.591	49.577	27.33
2400	HIS	N	30.272	24.958	47.865	29.80
2401	HIS	CA	29.907	23.613	47.358	33.13
2402	HIS	C	30.966	22.498	47.442	33.64
2403	HIS	O	31.210	21.764	46.489	31.30
2404	HIS	CB	29.302	23.669	45.909	36.51
2405	HIS	CG	28.204	24.708	45.783	40.71
2406	HIS	ND1	28.213	25.693	44.854	43.97
2407	HIS	CD2	27.063	24.893	46.600	42.68
2408	HIS	CE1	27.113	26.502	45.078	43.60
2409	HIS	NE2	26.408	26.006	46.157	42.67
2410	GLU	N	31.619	22.430	48.620	35.19
2411	GLU	CA	32.799	21.567	48.661	36.70
2412	GLU	C	32.611	20.063	48.720	38.60
2413	GLU	O	33.525	19.304	48.448	37.53
2414	GLU	CB	33.697	21.992	49.795	35.82
2415	GLU	CG	32.956	21.874	51.117	36.20
2416	GLU	CD	33.983	21.924	52.224	38.96
2417	GLU	OE1	34.913	22.725	52.123	36.60
2418	GLU	OE2	33.890	21.139	53.176	41.14
2419	ASP	N	31.402	19.658	49.089	42.63
2420	ASP	CA	31.156	18.226	49.154	46.40
2421	ASP	C	30.772	17.554	47.818	47.19
2422	ASP	O	30.066	18.144	46.977	46.38
2423	ASP	CB	30.260	17.938	50.394	50.98
2424	ASP	CG	31.161	17.875	51.659	57.85
2425	ASP	OD1	32.063	17.001	51.717	60.50

2426	ASP	OD2	30.999	18.696	52.591	61.02
2427	ASP	OXT	31.255	16.438	47.575	48.57
1	TIP3	OH2	60.719	23.664	43.966	20.00
2	TIP3	1H	60.985	23.573	44.873	20.00
3	TIP3	2H	60.658	24.587	43.766	20.00
4	TIP3	OH2	40.411	32.301	35.797	20.00
5	TIP3	1H	40.442	31.973	36.704	20.00
6	TIP3	2H	39.543	32.682	35.681	20.00
7	TIP3	OH2	45.842	40.160	69.804	20.00
8	TIP3	1H	46.390	40.196	70.592	20.00
9	TIP3	2H	46.479	40.472	69.181	20.00
10	TIP3	OH2	53.379	29.910	58.076	20.00
11	TIP3	1H	54.092	29.933	58.712	20.00
12	TIP3	2H	53.330	30.805	57.725	20.00
13	TIP3	OH2	65.665	24.233	43.388	20.00
14	TIP3	1H	66.318	23.787	43.947	20.00
15	TIP3	2H	66.089	25.124	43.306	20.00
16	TIP3	OH2	53.559	24.650	58.363	20.00
17	TIP3	1H	54.093	24.160	58.947	20.00
18	TIP3	2H	53.867	25.523	58.315	20.00
19	TIP3	OH2	64.454	48.312	45.244	20.00
20	TIP3	1H	64.267	48.158	46.175	20.00
21	TIP3	2H	63.857	49.038	45.064	20.00
22	TIP3	OH2	65.964	24.398	54.095	20.00
23	TIP3	1H	65.412	24.176	54.850	20.00
24	TIP3	2H	65.297	24.876	53.591	20.00
25	TIP3	OH2	45.682	25.930	65.899	20.00
26	TIP3	1H	46.136	26.039	66.729	20.00
27	TIP3	2H	45.378	26.840	65.851	20.00
28	TIP3	OH2	41.439	40.049	69.937	20.00
29	TIP3	1H	41.192	39.958	70.811	20.00
30	TIP3	2H	40.941	40.831	69.745	20.00
31	TIP3	OH2	44.346	6.948	53.731	20.00
32	TIP3	1H	44.331	7.414	54.574	20.00
33	TIP3	2H	43.897	7.661	53.211	20.00
34	TIP3	OH2	69.712	33.601	44.219	20.00
35	TIP3	1H	69.242	33.254	44.983	20.00
36	TIP3	2H	69.119	34.180	43.748	20.00
37	TIP3	OH2	58.068	40.012	37.522	20.00
38	TIP3	1H	57.605	39.244	37.688	20.00
39	TIP3	2H	57.929	40.200	36.598	20.00
40	TIP3	OH2	38.179	37.107	67.391	20.00
41	TIP3	1H	38.128	37.041	68.351	20.00
42	TIP3	2H	38.342	38.026	67.301	20.00
43	TIP3	OH2	53.580	42.001	38.764	20.00
44	TIP3	1H	53.963	41.667	39.579	20.00

45	TIP3	2H	53.329	42.839	39.103	20.00
46	TIP3	OH2	41.144	36.980	35.497	20.00
47	TIP3	1H	41.796	37.172	36.184	20.00
48	TIP3	2H	41.093	37.769	34.947	20.00
49	TIP3	OH2	63.542	14.613	42.941	20.00
50	TIP3	1H	63.904	14.292	43.762	20.00
51	TIP3	2H	63.730	15.559	42.948	20.00
52	TIP3	OH2	64.565	20.375	61.477	20.00
53	TIP3	1H	64.349	19.937	62.304	20.00
54	TIP3	2H	64.342	21.308	61.630	20.00
55	TIP3	OH2	73.801	37.858	38.356	20.00
56	TIP3	1H	73.658	37.517	39.241	20.00
57	TIP3	2H	73.755	38.813	38.502	20.00
58	TIP3	OH2	68.073	28.759	56.071	20.00
59	TIP3	1H	68.526	28.682	56.924	20.00
60	TIP3	2H	68.460	29.576	55.744	20.00
61	TIP3	OH2	66.813	32.500	36.292	20.00
62	TIP3	1H	66.619	33.294	36.779	20.00
63	TIP3	2H	67.059	32.915	35.452	20.00
64	TIP3	OH2	63.409	36.906	54.912	20.00
65	TIP3	1H	63.720	36.671	55.795	20.00
66	TIP3	2H	63.757	37.774	54.745	20.00
67	TIP3	OH2	75.979	37.116	45.918	20.00
68	TIP3	1H	75.933	36.923	46.791	20.00
69	TIP3	2H	75.587	37.969	45.865	20.00
70	TIP3	OH2	44.663	41.751	34.799	20.00
71	TIP3	1H	45.028	41.787	35.676	20.00
72	TIP3	2H	44.876	42.631	34.493	20.00
73	TIP3	OH2	26.251	25.219	59.180	20.00
74	TIP3	1H	26.739	25.004	59.969	20.00
75	TIP3	2H	26.454	26.133	58.987	20.00
76	TIP3	OH2	43.204	25.421	36.259	20.00
77	TIP3	1H	42.767	24.692	36.714	20.00
78	TIP3	2H	42.761	26.233	36.519	20.00
79	TIP3	OH2	48.443	47.491	57.210	20.00
80	TIP3	1H	48.360	47.421	58.167	20.00
81	TIP3	2H	48.503	48.418	56.985	20.00
82	TIP3	OH2	61.254	29.798	38.553	20.00
83	TIP3	1H	61.103	29.506	39.441	20.00
84	TIP3	2H	60.395	30.126	38.301	20.00
85	TIP3	OH2	76.145	33.804	35.273	20.00
86	TIP3	1H	76.871	33.620	35.878	20.00
87	TIP3	2H	76.462	34.565	34.787	20.00
88	TIP3	OH2	55.588	41.658	31.859	20.00
89	TIP3	1H	55.460	41.366	32.756	20.00
90	TIP3	2H	55.098	42.494	31.943	20.00

91	TIP3	OH2	44.487	25.053	41.030	20.00
92	TIP3	1H	44.965	24.874	41.840	20.00
93	TIP3	2H	43.913	25.788	41.262	20.00
94	TIP3	OH2	50.573	33.176	62.732	20.00
95	TIP3	1H	51.351	32.774	63.106	20.00
96	TIP3	2H	50.818	33.516	61.865	20.00
97	TIP3	OH2	49.953	52.982	34.749	20.00
98	TIP3	1H	49.992	52.859	35.691	20.00
99	TIP3	2H	49.758	53.917	34.634	20.00
100	TIP3	OH2	47.275	17.995	39.661	20.00
101	TIP3	1H	48.071	17.850	40.167	20.00
102	TIP3	2H	47.429	18.857	39.243	20.00
103	TIP3	OH2	71.352	29.089	36.878	20.00
104	TIP3	1H	71.322	29.074	37.839	20.00
105	TIP3	2H	71.180	29.979	36.603	20.00
106	TIP3	OH2	29.430	35.859	66.439	20.00
107	TIP3	1H	29.726	35.302	67.151	20.00
108	TIP3	2H	29.413	36.763	66.780	20.00
109	TIP3	OH2	60.271	6.760	44.654	20.00
110	TIP3	1H	60.468	6.649	45.591	20.00
111	TIP3	2H	60.190	7.711	44.594	20.00
112	TIP3	OH2	37.294	40.087	40.715	20.00
113	TIP3	1H	36.898	40.267	41.578	20.00
114	TIP3	2H	37.588	40.958	40.472	20.00
115	TIP3	OH2	43.748	16.614	44.085	20.00
116	TIP3	1H	44.120	16.513	44.960	20.00
117	TIP3	2H	43.925	17.542	44.004	20.00
118	TIP3	OH2	68.520	39.888	46.997	20.00
119	TIP3	1H	67.991	39.691	47.769	20.00
120	TIP3	2H	67.978	40.491	46.494	20.00
121	TIP3	OH2	58.983	37.779	38.817	20.00
122	TIP3	1H	59.166	37.703	39.753	20.00
123	TIP3	2H	58.959	38.722	38.652	20.00
1	NO_H	O1	56.508	33.999	33.158	0.00
2	NO_H	C2	56.195	34.428	34.475	0.00
3	NO_H	C3	55.272	33.387	34.975	0.00
4	NO_H	C4	55.005	32.237	34.328	0.00
5	NO_H	C5	55.802	31.748	33.139	0.00
6	NO_H	C6	57.040	32.661	33.064	0.00
7	NO_H	S11	54.303	33.664	36.352	0.00
8	NO_H	C12	53.738	31.989	36.222	0.00
9	NO_H	C13	54.015	31.430	35.040	0.00
10	NO_H	C14	53.373	30.194	34.527	0.00
11	NO_H	O15	53.544	29.898	33.386	0.00
12	NO_H	O16	52.655	29.368	35.270	0.00
13	NO_H	N17	52.959	31.222	37.208	0.00

14	NO_H	C18	52.258	31.692	38.256	0.00
15	NO_H	O19	52.471	32.753	38.871	0.00
16	NO_H	C20	51.099	30.781	38.736	0.00
17	NO_H	O21	50.031	31.233	39.053	0.00
18	NO_H	O22	51.286	29.429	38.924	0.00
19	NO_H	C23	55.687	35.865	34.517	0.00
20	NO_H	N25	56.853	36.772	34.366	0.00
21	NO_H	C31	57.312	37.239	33.194	0.00
22	NO_H	C32	58.507	38.073	33.403	0.00
23	NO_H	C33	58.662	38.076	34.763	0.00
24	NO_H	C34	57.674	37.221	35.392	0.00
25	NO_H	O35	57.690	36.879	36.554	0.00
26	NO_H	O36	56.825	36.836	32.137	0.00
27	NO_H	C37	59.400	38.796	32.575	0.00
28	NO_H	C38	60.492	39.457	33.192	0.00
29	NO_H	C39	60.621	39.444	34.609	0.00
30	NO_H	C40	59.698	38.714	35.403	0.00
31	NO_H	O44	61.631	40.169	35.326	0.00
32	NO_H	C45	61.145	40.731	36.599	0.00

TABLE C

Table of the orthogonal three dimensional coordinates in Ångstroms and B factors (Å^2) for Protein Tyrosine Phosphatase 1B complexed with 5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid (Example 4).

No	Amino acid		X	Y	Z	B
1	GLU	N	59.958	70.181	38.145	50.84
2	GLU	CA	58.803	69.268	38.132	51.38
3	GLU	C	58.809	68.319	36.855	49.72
4	GLU	O	59.460	68.640	35.857	49.04
5	GLU	CB	57.591	70.243	38.223	53.79
6	GLU	CG	56.243	69.633	38.610	57.54
7	GLU	CD	56.368	68.679	39.828	62.60
8	GLU	OE1	56.347	69.190	40.946	64.63
9	GLU	OE2	56.479	67.454	39.647	64.40
10	GLU	HA	58.898	68.637	39.019	20.00
11	GLU	1HB	57.526	70.850	37.323	20.00
12	GLU	2HB	57.818	70.928	39.043	20.00
13	GLU	1HG	55.736	69.097	37.823	20.00
14	GLU	2HG	55.552	70.439	38.879	20.00
15	MET	N	57.987	67.209	36.871	46.10
16	MET	CA	57.535	66.645	35.550	42.61
17	MET	C	56.699	67.639	34.673	40.49
18	MET	O	56.698	67.589	33.457	38.08
19	MET	CB	56.671	65.360	35.644	41.62
20	MET	CG	55.206	65.625	36.082	40.45
21	MET	SD	54.276	64.127	36.149	35.84
22	MET	CE	55.232	63.264	37.441	39.51
23	MET	H	57.559	66.997	37.759	20.00
24	MET	HA	58.440	66.400	35.000	20.00
25	MET	1HB	57.157	64.654	36.311	20.00
26	MET	2HB	56.626	64.870	34.671	20.00
27	MET	1HG	54.645	66.290	35.422	20.00
28	MET	2HG	55.188	66.074	37.082	20.00
29	MET	1HE	55.510	63.974	38.230	20.00
30	MET	2HE	56.154	62.833	37.052	20.00
31	MET	3HE	54.636	62.486	37.923	20.00
32	GLU	N	55.933	68.506	35.346	40.04
33	GLU	CA	55.048	69.427	34.645	41.99
34	GLU	C	55.841	70.396	33.686	41.64
35	GLU	O	55.416	70.753	32.599	42.33
36	GLU	CB	54.205	70.086	35.723	43.82
37	GLU	CG	52.967	70.759	35.105	47.17
38	GLU	CD	51.943	71.122	36.194	49.31
39	GLU	OE1	52.375	71.686	37.179	48.56
40	GLU	OE2	50.736	70.869	36.056	51.19
41	GLU	H	55.891	68.348	36.331	20.00
42	GLU	HA	54.387	68.813	34.030	20.00

43	GLU	1HB	54.780	70.799	36.314	20.00
44	GLU	2HB	53.860	69.333	36.440	20.00
45	GLU	1HG	52.473	70.118	34.379	20.00
46	GLU	2HG	53.234	71.688	34.607	20.00
47	LYS	N	57.077	70.711	34.138	40.99
48	LYS	CA	58.115	71.521	33.434	41.50
49	LYS	C	58.730	70.802	32.190	39.57
50	LYS	O	58.673	71.310	31.076	39.12
51	LYS	CB	59.261	71.933	34.428	45.89
52	LYS	CG	58.918	73.024	35.497	51.71
53	LYS	CD	59.986	73.136	36.630	56.13
54	LYS	CE	59.423	73.478	38.036	59.81
55	LYS	NZ	60.210	72.951	39.186	62.35
56	LYS	H	57.200	70.440	35.092	20.00
57	LYS	HA	57.601	72.409	33.064	20.00
58	LYS	1HB	60.122	72.290	33.861	20.00
59	LYS	2HB	59.590	71.028	34.944	20.00
60	LYS	1HG	57.935	72.822	35.923	20.00
61	LYS	2HG	58.812	73.990	35.000	20.00
62	LYS	1HD	60.756	73.854	36.348	20.00
63	LYS	2HD	60.497	72.177	36.711	20.00
64	LYS	1HE	58.404	73.085	38.137	20.00
65	LYS	2HE	59.313	74.564	38.135	20.00
66	LYS	1HZ	61.199	73.268	39.140	20.00
67	LYS	2HZ	60.194	71.902	39.141	20.00
68	LYS	3HZ	59.783	73.242	40.090	20.00
69	GLU	N	59.247	69.571	32.450	38.42
70	GLU	CA	59.583	68.656	31.386	37.30
71	GLU	C	58.523	68.608	30.274	34.58
72	GLU	O	58.814	68.798	29.094	33.74
73	GLU	CB	59.912	67.281	31.966	40.63
74	GLU	CG	60.000	66.235	30.835	46.16
75	GLU	CD	60.673	64.854	31.065	49.22
76	GLU	OE1	60.508	64.217	32.105	50.86
77	GLU	OE2	61.374	64.376	30.167	51.79
78	GLU	H	59.306	69.279	33.408	20.00
79	GLU	HA	60.487	69.052	30.916	20.00
80	GLU	1HB	59.208	66.970	32.737	20.00
81	GLU	2HB	60.879	67.339	32.462	20.00
82	GLU	1HG	60.482	66.668	29.959	20.00
83	GLU	2HG	58.967	66.050	30.534	20.00
84	PHE	N	57.266	68.373	30.681	31.46
85	PHE	CA	56.238	68.253	29.653	30.49
86	PHE	C	56.102	69.457	28.733	33.05
87	PHE	O	56.072	69.315	27.517	31.17
88	PHE	CB	54.928	67.999	30.280	26.00
89	PHE	CG	53.774	67.886	29.306	23.39
90	PHE	CD1	53.283	66.628	28.992	24.75
91	PHE	CD2	53.136	69.002	28.777	23.83
92	PHE	CE1	52.145	66.498	28.272	21.69
93	PHE	CE2	52.023	68.860	27.977	23.15
94	PHE	CZ	51.514	67.599	27.755	22.50

95	PHE	H	57.145	68.129	31.644	20.00
96	PHE	HA	56.531	67.409	29.021	20.00
97	PHE	1HB	54.687	68.795	30.988	20.00
98	PHE	2HB	54.998	67.080	30.860	20.00
99	PHE	HD1	53.805	65.747	29.338	20.00
100	PHE	HD2	53.488	70.001	29.012	20.00
101	PHE	HE1	51.759	65.506	28.091	20.00
102	PHE	HE2	51.544	69.725	27.536	20.00
103	PHE	HZ	50.632	67.461	27.165	20.00
104	GLU	N	56.018	70.665	29.336	34.78
105	GLU	CA	55.897	71.897	28.527	36.92
106	GLU	C	57.122	72.019	27.553	34.88
107	GLU	O	57.053	72.444	26.408	34.89
108	GLU	CB	55.852	73.091	29.484	42.69
109	GLU	CG	54.488	73.612	30.017	51.81
110	GLU	CD	54.564	75.215	30.166	58.22
111	GLU	OE1	55.679	75.818	30.045	60.76
112	GLU	OE2	53.497	75.845	30.355	60.88
113	GLU	H	55.958	70.729	30.335	20.00
114	GLU	HA	54.994	71.824	27.915	20.00
115	GLU	1HB	56.246	73.911	28.885	20.00
116	GLU	2HB	56.555	72.973	30.310	20.00
117	GLU	1HG	54.203	73.129	30.954	20.00
118	GLU	2HG	53.684	73.380	29.316	20.00
119	GLN	N	58.282	71.586	28.060	32.17
120	GLN	CA	59.556	71.631	27.323	32.79
121	GLN	C	59.615	70.636	26.126	32.59
122	GLN	O	60.173	71.008	25.095	33.38
123	GLN	CB	60.597	71.291	28.375	38.01
124	GLN	CG	62.059	71.020	27.998	46.72
125	GLN	CD	62.634	70.285	29.249	54.60
126	GLN	OE1	62.587	69.070	29.367	58.48
127	GLN	NE2	63.129	71.080	30.204	57.65
128	GLN	H	58.242	71.334	29.034	20.00
129	GLN	HA	59.693	72.651	26.984	20.00
130	GLN	1HB	60.256	70.391	28.865	20.00
131	GLN	2HB	60.549	72.041	29.167	20.00
132	GLN	1HG	62.601	71.953	27.837	20.00
133	GLN	2HG	62.187	70.379	27.126	20.00
134	GLN	1HE2	63.670	70.582	30.873	20.00
135	GLN	2HE2	62.955	72.054	30.303	20.00
136	ILE	N	59.048	69.416	26.317	30.75
137	ILE	CA	58.941	68.342	25.297	29.79
138	ILE	C	57.992	68.730	24.090	29.61
139	ILE	O	58.254	68.655	22.886	28.92
140	ILE	CB	58.520	66.966	25.824	28.01
141	ILE	CG1	59.648	66.484	26.709	26.65
142	ILE	CG2	58.389	65.988	24.623	24.67
143	ILE	CD1	59.272	65.414	27.633	30.61
144	ILE	H	58.661	69.264	27.231	20.00
145	ILE	HA	59.984	68.125	25.132	20.00
146	ILE	HB	57.585	67.027	26.380	20.00

147	ILE	1HG1	60.041	67.301	27.314	20.00
148	ILE	2HG1	60.483	66.163	26.083	20.00
149	ILE	1HG2	59.307	65.970	24.039	20.00
150	ILE	2HG2	57.582	66.246	23.946	20.00
151	ILE	3HG2	58.243	64.972	24.970	20.00
152	ILE	1HD1	58.868	64.551	27.108	20.00
153	ILE	2HD1	58.551	65.761	28.375	20.00
154	ILE	3HD1	60.223	65.162	28.094	20.00
155	ASP	N	56.856	69.222	24.608	30.56
156	ASP	CA	55.774	69.774	23.845	34.30
157	ASP	C	56.317	70.948	23.013	36.61
158	ASP	O	56.305	70.858	21.794	37.72
159	ASP	CB	54.623	70.039	24.829	34.23
160	ASP	CG	53.266	69.515	24.380	34.09
161	ASP	OD1	53.161	68.398	23.871	34.45
162	ASP	OD2	52.282	70.192	24.584	35.24
163	ASP	H	56.711	69.214	25.597	20.00
164	ASP	HA	55.509	68.998	23.135	20.00
165	ASP	1HB	54.530	71.096	25.058	20.00
166	ASP	2HB	54.782	69.545	25.769	20.00
167	LYS	N	56.891	71.996	23.669	38.57
168	LYS	CA	57.394	73.143	22.870	40.78
169	LYS	C	58.187	72.746	21.598	40.89
170	LYS	O	57.821	73.058	20.475	41.19
171	LYS	CB	58.195	74.152	23.704	44.73
172	LYS	CG	59.737	74.010	23.716	49.46
173	LYS	CD	60.389	74.662	24.948	52.61
174	LYS	CE	61.863	74.244	25.156	51.86
175	LYS	NZ	62.098	72.811	24.890	49.92
176	LYS	H	56.748	71.985	24.653	20.00
177	LYS	HA	56.492	73.642	22.511	20.00
178	LYS	1HB	57.810	74.129	24.724	20.00
179	LYS	2HB	57.962	75.153	23.339	20.00
180	LYS	1HG	60.175	74.398	22.793	20.00
181	LYS	2HG	59.978	72.965	23.809	20.00
182	LYS	1HD	59.811	74.375	25.827	20.00
183	LYS	2HD	60.301	75.749	24.895	20.00
184	LYS	1HE	62.176	74.480	26.182	20.00
185	LYS	2HE	62.505	74.843	24.502	20.00
186	LYS	1HZ	61.912	72.594	23.887	20.00
187	LYS	2HZ	61.421	72.194	25.397	20.00
188	LYS	3HZ	63.067	72.497	25.108	20.00
189	SER	N	59.282	72.003	21.844	39.93
190	SER	CA	60.160	71.674	20.742	41.11
191	SER	C	59.713	70.466	19.823	41.60
192	SER	O	60.502	69.985	19.006	44.13
193	SER	CB	61.342	71.196	21.527	41.13
194	SER	OG	60.972	70.326	22.646	43.06
195	SER	H	59.394	71.615	22.757	20.00
196	SER	HA	60.414	72.549	20.149	20.00
197	SER	1HB	61.840	72.111	21.923	20.00
198	SER	2HB	62.201	70.871	20.872	20.00

199	SER	HG	60.144	69.739	22.668	20.00
200	GLY	N	58.471	69.970	20.020	39.95
201	GLY	CA	58.004	68.791	19.312	36.83
202	GLY	C	58.868	67.488	19.463	35.39
203	GLY	O	59.151	66.807	18.529	37.15
204	GLY	H	57.818	70.556	20.489	20.00
205	GLY	1HA	57.969	69.018	18.241	20.00
206	GLY	2HA	57.004	68.542	19.656	20.00
207	SER	N	59.300	67.067	20.659	32.66
208	SER	CA	60.096	65.891	20.842	31.67
209	SER	C	59.562	64.556	21.564	29.26
210	SER	O	60.362	63.696	21.864	28.04
211	SER	CB	61.523	66.205	21.262	32.05
212	SER	OG	61.785	67.365	22.072	36.33
213	SER	H	58.976	67.617	21.428	20.00
214	SER	HA	60.276	65.532	19.858	20.00
215	SER	1HB	62.162	66.169	20.334	20.00
216	SER	2HB	61.990	65.313	21.767	20.00
217	SER	HG	61.143	68.124	22.244	20.00
218	TRP	N	58.263	64.341	21.705	26.65
219	TRP	CA	57.678	63.094	22.236	21.95
220	TRP	C	58.092	61.836	21.456	21.43
221	TRP	O	58.398	60.796	21.999	21.86
222	TRP	CB	56.162	63.309	22.226	22.70
223	TRP	CG	55.712	64.329	23.250	20.91
224	TRP	CD1	55.145	65.601	23.071	21.20
225	TRP	CD2	55.791	64.152	24.658	21.02
226	TRP	NE1	54.895	66.197	24.287	21.97
227	TRP	CE2	55.270	65.323	25.295	20.57
228	TRP	CE3	56.277	63.109	25.402	18.68
229	TRP	CZ2	55.184	65.387	26.676	20.86
230	TRP	CZ3	56.215	63.188	26.788	16.67
231	TRP	CH2	55.658	64.311	27.429	19.85
232	TRP	H	57.686	65.143	21.597	20.00
233	TRP	HA	58.058	62.950	23.247	20.00
234	TRP	1HB	55.644	62.373	22.446	20.00
235	TRP	2HB	55.835	63.613	21.232	20.00
236	TRP	HD1	54.914	66.062	22.121	20.00
237	TRP	HE1	54.495	67.092	24.417	20.00
238	TRP	HE3	56.679	62.229	24.906	20.00
239	TRP	HZ2	54.819	66.296	27.119	20.00
240	TRP	HZ3	56.622	62.372	27.369	20.00
241	TRP	HH2	55.652	64.334	28.506	20.00
242	ALA	N	58.142	61.898	20.137	21.75
243	ALA	CA	58.747	60.754	19.397	21.29
244	ALA	C	60.219	60.530	19.762	19.48
245	ALA	O	60.614	59.444	20.080	17.73
246	ALA	CB	58.536	60.943	17.876	21.57
247	ALA	H	57.792	62.693	19.657	20.00
248	ALA	HA	58.226	59.852	19.697	20.00
249	ALA	1HB	59.132	61.760	17.471	20.00
250	ALA	2HB	57.493	61.183	17.683	20.00

251	ALA	3HB	5[illegible]89	60.035	17.340	[illegible].00
252	ALA	N	61.000	61.573	19.777	21.34
253	ALA	CA	62.397	61.371	20.129	20.36
254	ALA	C	62.640	60.772	21.579	20.18
255	ALA	O	63.307	59.773	21.765	23.47
256	ALA	CB	62.920	62.788	20.000	21.69
257	ALA	H	60.646	62.340	19.255	20.00
258	ALA	HA	62.858	60.692	19.413	20.00
259	ALA	1HB	62.433	63.449	20.701	20.00
260	ALA	2HB	62.763	63.151	18.988	20.00
261	ALA	3HB	63.990	62.798	20.177	20.00
262	ILE	N	61.932	61.425	22.576	20.36
263	ILE	CA	61.790	60.947	23.989	20.21
264	ILE	C	61.398	59.404	24.061	19.21
265	ILE	O	62.077	58.599	24.654	20.20
266	ILE	CB	60.737	61.851	24.792	21.58
267	ILE	CG1	60.968	63.384	24.927	25.33
268	ILE	CG2	60.518	61.317	26.196	23.50
269	ILE	CD1	62.410	63.607	25.264	26.28
270	ILE	H	61.488	62.254	22.255	20.00
271	ILE	HA	62.789	61.058	24.405	20.00
272	ILE	HB	59.791	61.736	24.267	20.00
273	ILE	1HG1	60.325	63.814	25.692	20.00
274	ILE	2HG1	60.743	63.949	24.032	20.00
275	ILE	1HG2	61.434	61.342	26.788	20.00
276	ILE	2HG2	60.157	60.290	26.217	20.00
277	ILE	3HG2	59.791	61.912	26.743	20.00
278	ILE	1HD1	63.073	63.217	24.492	20.00
279	ILE	2HD1	62.691	63.122	26.198	20.00
280	ILE	3HD1	62.627	64.673	25.357	20.00
281	TYR	N	60.231	59.064	23.403	18.90
282	TYR	CA	59.663	57.728	23.212	16.59
283	TYR	C	60.620	56.761	22.628	19.69
284	TYR	O	60.722	55.641	23.044	21.05
285	TYR	CB	58.346	57.810	22.413	15.48
286	TYR	CG	57.722	56.420	22.275	15.58
287	TYR	CD1	57.298	55.713	23.438	15.71
288	TYR	CD2	57.586	55.775	21.044	17.07
289	TYR	CE1	56.771	54.396	23.415	15.33
290	TYR	CE2	57.097	54.458	20.983	18.24
291	TYR	CZ	56.694	53.755	22.144	17.83
292	TYR	OH	56.243	52.455	21.973	16.43
293	TYR	H	59.824	59.847	22.928	20.00
294	TYR	HA	59.466	57.370	24.214	20.00
295	TYR	1HB	58.526	58.248	21.425	20.00
296	TYR	2HB	57.651	58.450	22.951	20.00
297	TYR	HD1	57.367	56.218	24.392	20.00
298	TYR	HD2	57.892	56.285	20.136	20.00
299	TYR	HE1	56.386	54.090	24.384	20.00
300	TYR	HE2	56.999	53.996	20.016	20.00
301	TYR	HH	56.824	51.863	22.447	20.00
302	GLN	N	61.366	57.183	21.632	20.71

303	GLN	CA	62.[illegible]79	56.353	21.092	2[illegible].54
304	GLN	C	63.491	56.092	22.091	21.33
305	GLN	O	63.866	54.931	22.226	22.52
306	GLN	CB	62.737	56.837	19.717	29.74
307	GLN	CG	61.480	56.551	18.818	43.77
308	GLN	CD	61.124	57.664	17.789	50.76
309	GLN	OE1	61.317	58.863	17.906	53.37
310	GLN	NE2	60.647	57.254	16.639	51.41
311	GLN	H	61.282	58.134	21.330	20.00
312	GLN	HA	61.918	55.375	20.947	20.00
313	GLN	1HB	63.576	56.262	19.335	20.00
314	GLN	2HB	63.034	57.885	19.731	20.00
315	GLN	1HG	60.567	56.384	19.385	20.00
316	GLN	2HG	61.648	55.643	18.247	20.00
317	GLN	1HE2	60.739	58.175	16.252	20.00
318	GLN	2HE2	60.319	56.444	16.170	20.00
319	ASP	N	63.890	57.146	22.820	22.69
320	ASP	CA	64.915	56.979	23.869	23.75
321	ASP	C	64.453	55.995	24.956	21.78
322	ASP	O	65.227	55.192	25.428	21.26
323	ASP	CB	65.301	58.315	24.526	26.73
324	ASP	CG	65.718	59.428	23.564	31.02
325	ASP	OD1	66.369	59.105	22.550	31.00
326	ASP	OD2	65.408	60.604	23.837	32.48
327	ASP	H	63.674	58.089	22.539	20.00
328	ASP	HA	65.794	56.545	23.392	20.00
329	ASP	1HB	66.116	58.169	25.233	20.00
330	ASP	2HB	64.466	58.694	25.112	20.00
331	ILE	N	63.136	56.005	25.269	20.63
332	ILE	CA	62.626	54.892	26.106	19.38
333	ILE	C	62.664	53.512	25.346	19.66
334	ILE	O	63.081	52.492	25.913	18.07
335	ILE	CB	61.192	55.230	26.721	19.75
336	ILE	CG1	61.197	56.210	27.894	19.61
337	ILE	CG2	60.570	54.008	27.384	16.65
338	ILE	CD1	59.917	57.001	28.052	21.44
339	ILE	H	62.684	56.835	24.927	20.00
340	ILE	HA	63.327	54.768	26.932	20.00
341	ILE	HB	60.568	55.595	25.907	20.00
342	ILE	1HG1	61.987	56.937	27.696	20.00
343	ILE	2HG1	61.490	55.748	28.838	20.00
344	ILE	1HG2	61.179	53.628	28.194	20.00
345	ILE	2HG2	60.422	53.213	26.655	20.00
346	ILE	3HG2	59.582	54.249	27.768	20.00
347	ILE	1HD1	59.114	56.434	28.480	20.00
348	ILE	2HD1	59.594	57.364	27.080	20.00
349	ILE	3HD1	60.051	57.880	28.668	20.00
350	ARG	N	62.162	53.475	24.066	19.64
351	ARG	CA	62.288	52.251	23.267	22.20
352	ARG	C	63.742	51.742	23.370	22.74
353	ARG	O	63.964	50.589	23.705	20.20
354	ARG	CB	61.788	52.370	21.795	23.80

355	ARG	CG	60.263	52.326	21.416	2[illegible].28
356	ARG	CD	59.846	51.717	19.966	38.17
357	ARG	NE	58.356	51.345	19.989	47.71
358	ARG	CZ	57.194	51.166	19.228	46.22
359	ARG	NH1	57.118	51.134	17.914	51.10
360	ARG	NH2	56.016	50.979	19.791	39.82
361	ARG	H	61.917	54.354	23.659	20.00
362	ARG	HA	61.656	51.528	23.768	20.00
363	ARG	1HB	62.257	51.547	21.248	20.00
364	ARG	2HB	62.258	53.237	21.335	20.00
365	ARG	1HG	59.801	53.297	21.613	20.00
366	ARG	2HG	59.896	51.626	22.154	20.00
367	ARG	1HD	60.387	50.786	19.796	20.00
368	ARG	2HD	60.080	52.412	19.161	20.00
369	ARG	HE	58.008	51.167	20.902	20.00
370	ARG	1HH1	56.227	51.223	17.478	20.00
371	ARG	2HH1	57.905	50.928	17.355	20.00
372	ARG	1HH2	55.262	50.537	19.303	20.00
373	ARG	2HH2	55.845	51.282	20.734	20.00
374	HIS	N	64.746	52.610	23.202	20.00
375	HIS	CA	66.074	51.898	23.241	20.00
376	HIS	C	66.658	51.767	24.678	20.00
377	HIS	O	67.428	50.861	24.973	20.00
378	HIS	CB	67.188	52.616	22.410	20.00
379	HIS	CG	66.701	53.751	21.532	20.00
380	HIS	ND1	66.063	53.572	20.339	20.00
381	HIS	CD2	66.954	55.115	21.693	20.00
382	HIS	CE1	65.963	54.797	19.797	20.00
383	HIS	NE2	66.488	55.736	20.591	20.00
384	HIS	H	64.728	53.577	22.922	20.00
385	HIS	HA	65.925	50.904	22.851	20.00
386	HIS	1HB	67.950	53.016	23.105	20.00
387	HIS	2HB	67.710	51.887	21.787	20.00
388	HIS	HD1	65.792	52.727	19.934	20.00
389	HIS	HD2	67.557	55.565	22.468	20.00
390	HIS	HE1	65.731	54.961	18.764	20.00
391	GLU	N	66.332	52.581	25.699	24.60
392	GLU	CA	66.817	52.241	27.039	23.35
393	GLU	C	66.236	50.854	27.523	20.84
394	GLU	O	66.743	50.234	28.462	20.77
395	GLU	CB	66.563	53.445	27.980	25.78
396	GLU	CG	67.579	54.531	27.671	34.71
397	GLU	CD	67.550	55.857	28.464	41.97
398	GLU	OE1	67.473	55.873	29.688	47.08
399	GLU	OE2	67.723	56.887	27.831	42.03
400	GLU	H	65.826	53.435	25.569	20.00
401	GLU	HA	67.896	52.124	26.937	20.00
402	GLU	1HB	66.656	53.140	29.019	20.00
403	GLU	2HB	65.552	53.848	27.866	20.00
404	GLU	1HG	67.556	54.790	26.615	20.00
405	GLU	2HG	68.561	54.116	27.863	20.00
406	ALA	N	65.138	50.381	26.878	20.22

407	ALA	CA	64.425	49.305	27.596	[illegible].85
408	ALA	C	65.171	47.952	27.675	19.60
409	ALA	O	66.080	47.612	26.913	21.31
410	ALA	CB	62.979	49.307	27.198	17.65
411	ALA	H	64.736	50.905	26.129	20.00
412	ALA	HA	64.411	49.635	28.630	20.00
413	ALA	1HB	62.886	49.086	26.128	20.00
414	ALA	2HB	62.566	50.300	27.380	20.00
415	ALA	3HB	62.406	48.566	27.755	20.00
416	SER	N	64.735	47.217	28.738	17.44
417	SER	CA	65.303	45.958	29.138	17.65
418	SER	C	65.080	44.926	28.069	20.44
419	SER	O	64.118	44.975	27.295	20.82
420	SER	CB	64.662	45.552	30.486	16.87
421	SER	OG	64.525	46.634	31.510	17.03
422	SER	H	63.945	47.581	29.221	20.00
423	SER	HA	66.386	46.074	29.221	20.00
424	SER	1HB	65.308	44.740	30.885	20.00
425	SER	2HB	63.712	44.975	30.299	20.00
426	SER	HG	64.529	47.621	31.322	20.00
427	ASP	N	65.958	43.934	28.082	23.65
428	ASP	CA	65.585	42.963	27.136	25.32
429	ASP	C	66.051	41.684	27.689	24.00
430	ASP	O	67.238	41.557	27.964	25.47
431	ASP	CB	66.321	43.342	25.827	30.03
432	ASP	CG	66.013	42.208	24.837	35.94
433	ASP	OD1	64.835	41.789	24.742	37.82
434	ASP	OD2	66.971	41.731	24.221	40.50
435	ASP	H	66.864	43.946	28.494	20.00
436	ASP	HA	64.508	42.853	26.973	20.00
437	ASP	1HB	67.406	43.380	25.994	20.00
438	ASP	2HB	66.013	44.285	25.384	20.00
439	PHE	N	65.113	40.763	27.872	20.26
440	PHE	CA	65.402	39.506	28.474	17.74
441	PHE	C	64.786	38.500	27.583	19.63
442	PHE	O	63.886	38.850	26.811	18.88
443	PHE	CB	64.780	39.359	29.899	15.74
444	PHE	CG	65.255	40.400	30.868	14.99
445	PHE	CD1	66.433	40.210	31.547	14.29
446	PHE	CD2	64.503	41.531	31.095	11.07
447	PHE	CE1	66.871	41.163	32.441	13.28
448	PHE	CE2	64.910	42.478	32.012	12.04
449	PHE	CZ	66.114	42.290	32.698	14.86
450	PHE	H	64.258	40.990	27.405	20.00
451	PHE	HA	66.483	39.375	28.481	20.00
452	PHE	1HB	64.945	38.372	30.333	20.00
453	PHE	2HB	63.697	39.445	29.816	20.00
454	PHE	HD1	67.024	39.314	31.395	20.00
455	PHE	HD2	63.562	41.653	30.585	20.00
456	PHE	HE1	67.800	41.004	32.982	20.00
457	PHE	HE2	64.290	43.328	32.250	20.00
458	PHE	HZ	66.455	43.015	33.431	20.00

459	PRO	N	6[illegible].253	37.196	27.759	[illegible].03
460	PRO	CA	64.636	36.040	27.082	17.74
461	PRO	C	63.151	35.749	27.411	17.59
462	PRO	O	62.694	35.796	28.535	18.11
463	PRO	CB	65.582	34.833	27.412	17.29
464	PRO	CG	66.564	35.298	28.571	17.67
465	PRO	CD	66.467	36.813	28.562	17.97
466	PRO	HA	64.674	36.227	26.012	20.00
467	PRO	1HB	66.190	34.622	26.529	20.00
468	PRO	2HB	65.034	33.928	27.683	20.00
469	PRO	1HG	66.200	34.943	29.539	20.00
470	PRO	2HG	67.592	34.936	28.459	20.00
471	PRO	1HD	67.323	37.192	28.014	20.00
472	PRO	2HD	66.501	37.258	29.556	20.00
473	CYS	N	62.429	35.432	26.359	16.91
474	CYS	CA	61.116	34.821	26.476	16.83
475	CYS	C	61.155	33.441	25.799	17.10
476	CYS	O	60.446	33.139	24.838	15.98
477	CYS	CB	60.141	35.734	25.788	17.42
478	CYS	SG	60.311	37.521	26.025	21.76
479	CYS	H	62.845	35.661	25.483	20.00
480	CYS	HA	60.833	34.706	27.525	20.00
481	CYS	1HB	59.112	35.435	26.009	20.00
482	CYS	2HB	60.247	35.600	24.709	20.00
483	CYS	HG	61.234	38.020	25.205	20.00
484	ARG	N	62.055	32.618	26.311	17.15
485	ARG	CA	62.240	31.246	25.729	19.32
486	ARG	C	61.030	30.297	25.783	19.49
487	ARG	O	60.747	29.643	24.808	19.32
488	ARG	CB	63.463	30.474	26.274	24.18
489	ARG	CG	64.803	30.648	25.474	34.75
490	ARG	CD	66.027	31.366	26.089	42.80
491	ARG	NE	65.822	31.308	27.538	51.13
492	ARG	CZ	66.692	31.456	28.527	51.47
493	ARG	NH1	67.986	31.573	28.252	48.86
494	ARG	NH2	66.143	31.494	29.730	48.27
495	ARG	H	62.418	32.881	27.211	20.00
496	ARG	HA	62.407	31.422	24.671	20.00
497	ARG	1HB	63.253	29.408	26.156	20.00
498	ARG	2HB	63.503	30.537	27.360	20.00
499	ARG	1HG	64.620	31.011	24.461	20.00
500	ARG	2HG	65.175	29.633	25.308	20.00
501	ARG	1HD	66.058	32.421	25.820	20.00
502	ARG	2HD	66.979	30.904	25.819	20.00
503	ARG	HE	64.881	31.300	27.880	20.00
504	ARG	1HH1	68.672	31.709	28.970	20.00
505	ARG	2HH1	68.274	31.511	27.301	20.00
506	ARG	1HH2	66.703	31.481	30.549	20.00
507	ARG	2HH2	65.138	31.551	29.794	20.00
508	VAL	N	60.319	30.155	26.945	17.97
509	VAL	CA	59.174	29.238	26.975	16.80
510	VAL	C	58.113	29.793	26.009	15.05

511	VAL	O	57.497	29.009	25.329	1[illegible].45
512	VAL	CB	58.828	28.750	28.462	18.01
513	VAL	CG1	57.372	28.681	28.911	15.99
514	VAL	CG2	59.711	29.222	29.601	17.07
515	VAL	H	60.614	30.724	27.716	20.00
516	VAL	HA	59.553	28.350	26.498	20.00
517	VAL	HB	59.085	27.690	28.412	20.00
518	VAL	1HG1	56.744	28.248	28.134	20.00
519	VAL	2HG1	56.988	29.671	29.154	20.00
520	VAL	3HG1	57.249	28.037	29.790	20.00
521	VAL	1HG2	59.485	30.243	29.907	20.00
522	VAL	2HG2	60.768	29.174	29.338	20.00
523	VAL	3HG2	59.588	28.576	30.471	20.00
524	ALA	N	57.929	31.159	25.879	14.53
525	ALA	CA	56.893	31.736	24.965	14.43
526	ALA	C	57.034	31.215	23.579	15.46
527	ALA	O	56.026	30.897	22.995	16.10
528	ALA	CB	56.950	33.283	24.793	12.61
529	ALA	H	58.489	31.728	26.477	20.00
530	ALA	HA	55.936	31.377	25.317	20.00
531	ALA	1HB	57.978	33.586	24.605	20.00
532	ALA	2HB	56.694	33.786	25.717	20.00
533	ALA	3HB	56.439	33.685	23.923	20.00
534	LYS	N	58.297	31.191	23.122	17.52
535	LYS	CA	58.835	30.716	21.906	17.70
536	LYS	C	58.993	29.228	21.723	19.60
537	LYS	O	59.486	28.823	20.702	22.60
538	LYS	CB	60.168	31.413	21.780	19.24
539	LYS	CG	60.083	32.927	21.737	19.97
540	LYS	CD	59.064	33.361	20.674	21.69
541	LYS	CE	59.193	34.787	20.078	24.74
542	LYS	NZ	58.108	35.143	19.082	26.46
543	LYS	H	58.962	31.547	23.782	20.00
544	LYS	HA	58.145	31.021	21.117	20.00
545	LYS	1HB	60.687	31.055	20.890	20.00
546	LYS	2HB	60.838	31.130	22.595	20.00
547	LYS	1HG	61.064	33.367	21.526	20.00
548	LYS	2HG	59.740	33.340	22.686	20.00
549	LYS	1HD	58.049	33.228	21.050	20.00
550	LYS	2HD	59.142	32.677	19.824	20.00
551	LYS	1HE	60.168	34.871	19.582	20.00
552	LYS	2HE	59.209	35.527	20.883	20.00
553	LYS	1HZ	57.167	35.181	19.539	20.00
554	LYS	2HZ	58.096	34.490	18.275	20.00
555	LYS	3HZ	58.222	36.119	18.723	20.00
556	LEU	N	58.600	28.321	22.639	20.39
557	LEU	CA	58.649	26.874	22.415	19.13
558	LEU	C	57.499	26.495	21.561	21.96
559	LEU	O	56.401	27.065	21.641	20.82
560	LEU	CB	58.382	26.108	23.763	18.89
561	LEU	CG	59.526	26.182	24.733	17.87
562	LEU	CD1	60.698	25.466	24.168	19.14

563	LEU	CD2	59.172	25.541	26.090	17.39
564	LEU	H	58.246	28.683	23.495	20.00
565	LEU	HA	59.615	26.655	21.958	20.00
566	LEU	1HB	58.175	25.056	23.593	20.00
567	LEU	2HB	57.485	26.522	24.240	20.00
568	LEU	HG	59.806	27.235	24.855	20.00
569	LEU	1HD1	61.105	25.936	23.272	20.00
570	LEU	2HD1	60.454	24.433	23.933	20.00
571	LEU	3HD1	61.510	25.440	24.897	20.00
572	LEU	1HD2	58.924	24.482	25.978	20.00
573	LEU	2HD2	58.292	26.034	26.506	20.00
574	LEU	3HD2	59.988	25.638	26.811	20.00
575	PRO	N	57.678	25.487	20.700	23.61
576	PRO	CA	56.624	25.246	19.703	24.44
577	PRO	C	55.294	24.893	20.278	22.23
578	PRO	O	54.301	25.224	19.668	23.82
579	PRO	CB	57.127	24.113	18.808	26.16
580	PRO	CG	58.632	24.213	19.010	27.75
581	PRO	CD	58.950	24.825	20.348	26.72
582	PRO	HA	56.514	26.154	19.103	20.00
583	PRO	1HB	56.822	24.188	17.756	20.00
584	PRO	2HB	56.800	23.128	19.167	20.00
585	PRO	1HG	59.145	23.261	18.859	20.00
586	PRO	2HG	59.017	24.887	18.240	20.00
587	PRO	1HD	59.763	25.549	20.239	20.00
588	PRO	2HD	59.256	24.094	21.089	20.00
589	LYS	N	55.275	24.280	21.486	22.30
590	LYS	CA	53.990	23.915	22.172	22.26
591	LYS	C	53.174	25.094	22.666	22.91
592	LYS	O	51.958	24.974	22.806	25.95
593	LYS	CB	54.084	22.876	23.305	23.13
594	LYS	CG	54.925	23.304	24.549	24.19
595	LYS	CD	54.938	22.261	25.694	27.45
596	LYS	CE	55.785	22.825	26.873	31.65
597	LYS	NZ	55.815	22.067	28.141	37.10
598	LYS	H	56.127	23.877	21.799	20.00
599	LYS	HA	53.394	23.472	21.378	20.00
600	LYS	1HB	54.522	21.963	22.895	20.00
601	LYS	2HB	53.080	22.604	23.629	20.00
602	LYS	1HG	54.556	24.257	24.934	20.00
603	LYS	2HG	55.948	23.498	24.234	20.00
604	LYS	1HD	55.299	21.288	25.356	20.00
605	LYS	2HD	53.903	22.109	26.017	20.00
606	LYS	1HE	55.373	23.814	27.106	20.00
607	LYS	2HE	56.810	23.019	26.530	20.00
608	LYS	1HZ	56.128	21.082	28.050	20.00
609	LYS	2HZ	54.827	22.030	28.497	20.00
610	LYS	3HZ	56.381	22.529	28.880	20.00
611	ASN	N	53.890	26.227	22.879	20.49
612	ASN	CA	53.214	27.434	23.253	18.95
613	ASN	C	52.746	28.350	22.087	19.83
614	ASN	O	52.113	29.392	22.300	16.61

615	ASN	CB	54.191	28.118	24.160	15.32
616	ASN	CG	54.146	27.319	25.455	18.08
617	ASN	OD1	53.155	26.658	25.743	16.89
618	ASN	ND2	55.231	27.426	26.237	17.04
619	ASN	H	54.866	26.232	22.663	20.00
620	ASN	HA	52.284	27.169	23.748	20.00
621	ASN	1HB	53.876	29.132	24.406	20.00
622	ASN	2HB	55.207	28.155	23.763	20.00
623	ASN	1HD2	55.118	26.972	27.105	20.00
624	ASN	2HD2	56.036	27.928	25.914	20.00
625	LYS	N	53.052	27.988	20.818	19.50
626	LYS	CA	52.880	28.993	19.736	20.65
627	LYS	C	51.462	29.515	19.709	17.99
628	LYS	O	51.176	30.690	19.685	17.79
629	LYS	CB	53.224	28.321	18.344	24.77
630	LYS	CG	53.732	29.255	17.235	35.23
631	LYS	CD	54.019	28.612	15.850	43.17
632	LYS	CE	54.433	29.635	14.731	48.79
633	LYS	NZ	54.133	29.061	13.411	51.89
634	LYS	H	53.580	27.148	20.703	20.00
635	LYS	HA	53.557	29.817	19.962	20.00
636	LYS	1HB	52.351	27.791	17.957	20.00
637	LYS	2HB	53.960	27.534	18.498	20.00
638	LYS	1HG	54.655	29.727	17.587	20.00
639	LYS	2HG	53.003	30.061	17.104	20.00
640	LYS	1HD	53.098	28.115	15.541	20.00
641	LYS	2HD	54.759	27.817	15.949	20.00
642	LYS	1HE	55.496	29.890	14.790	20.00
643	LYS	2HE	53.870	30.569	14.815	20.00
644	LYS	1HZ	53.097	29.011	13.287	20.00
645	LYS	2HZ	54.453	28.080	13.339	20.00
646	LYS	3HZ	54.503	29.603	12.605	20.00
647	ASN	N	50.566	28.527	19.762	16.87
648	ASN	CA	49.107	28.843	19.726	17.37
649	ASN	C	48.464	29.507	21.029	14.52
650	ASN	O	47.248	29.727	21.164	14.87
651	ASN	CB	48.373	27.533	19.306	17.56
652	ASN	CG	48.272	26.488	20.402	21.16
653	ASN	OD1	48.877	26.514	21.451	23.28
654	ASN	ND2	47.525	25.472	20.024	22.37
655	ASN	H	50.925	27.620	19.959	20.00
656	ASN	HA	48.961	29.568	18.921	20.00
657	ASN	1HB	48.842	27.093	18.437	20.00
658	ASN	2HB	47.350	27.783	19.013	20.00
659	ASN	1HD2	47.520	24.710	20.667	20.00
660	ASN	2HD2	47.013	25.510	19.175	20.00
661	ARG	N	49.398	29.743	21.971	13.45
662	ARG	CA	49.080	30.421	23.219	14.08
663	ARG	C	49.442	31.897	23.164	11.72
664	ARG	O	49.239	32.606	24.120	11.90
665	ARG	CB	49.812	29.746	24.405	14.72
666	ARG	CG	49.139	28.440	24.752	15.03

667	ARG	CD	49.763	27.746	25.988	13.22
668	ARG	NE	48.959	26.521	26.267	14.96
669	ARG	CZ	48.858	25.909	27.402	15.87
670	ARG	NH1	49.281	26.474	28.507	14.76
671	ARG	NH2	48.299	24.741	27.436	16.81
672	ARG	H	50.337	29.472	21.776	20.00
673	ARG	HA	48.004	30.372	23.369	20.00
674	ARG	1HB	49.727	30.401	25.279	20.00
675	ARG	2HB	50.877	29.631	24.213	20.00
676	ARG	1HG	49.197	27.772	23.893	20.00
677	ARG	2HG	48.078	28.628	24.920	20.00
678	ARG	1HD	49.685	28.396	26.850	20.00
679	ARG	2HD	50.798	27.458	25.812	20.00
680	ARG	HE	48.517	26.130	25.480	20.00
681	ARG	1HH1	49.168	26.032	29.395	20.00
682	ARG	2HH1	49.705	27.377	28.439	20.00
683	ARG	1HH2	48.173	24.251	28.303	20.00
684	ARG	2HH2	47.960	24.316	26.599	20.00
685	ASN	N	49.996	32.318	22.035	12.70
686	ASN	CA	50.406	33.706	21.870	12.44
687	ASN	C	49.508	34.267	20.783	12.58
688	ASN	O	49.360	33.682	19.731	11.79
689	ASN	CB	51.893	33.770	21.499	15.34
690	ASN	CG	52.706	33.250	22.622	15.14
691	ASN	OD1	52.540	33.681	23.718	13.40
692	ASN	ND2	53.664	32.406	22.420	15.01
693	ASN	H	50.101	31.681	21.265	20.00
694	ASN	HA	50.227	34.257	22.794	20.00
695	ASN	1HB	52.211	34.789	21.274	20.00
696	ASN	2HB	52.099	33.162	20.620	20.00
697	ASN	1HD2	54.227	32.167	23.194	20.00
698	ASN	2HD2	53.844	32.004	21.533	20.00
699	ARG	N	48.922	35.407	21.070	11.31
700	ARG	CA	48.157	36.050	20.031	10.21
701	ARG	C	49.030	36.735	18.938	11.77
702	ARG	O	48.660	36.681	17.785	10.43
703	ARG	CB	47.337	37.044	20.779	10.53
704	ARG	CG	46.560	37.866	19.869	9.14
705	ARG	CD	45.810	38.876	20.590	10.01
706	ARG	NE	44.644	38.387	21.426	10.47
707	ARG	CZ	43.536	38.042	20.725	10.78
708	ARG	NH1	43.385	38.316	19.382	11.53
709	ARG	NH2	42.642	37.281	21.300	10.00
710	ARG	H	48.857	35.623	22.040	20.00
711	ARG	HA	47.516	35.294	19.567	20.00
712	ARG	1HB	47.990	37.689	21.376	20.00
713	ARG	2HB	46.686	36.526	21.493	20.00
714	ARG	1HG	45.916	37.234	19.260	20.00
715	ARG	2HG	47.204	38.380	19.156	20.00
716	ARG	1HD	45.508	39.367	19.671	20.00
717	ARG	2HD	46.466	39.497	21.205	20.00
718	ARG	HE	44.748	38.186	22.399	20.00

719	ARG	1HH1	42.596	37.960	18.878	20.00
720	ARG	2HH1	44.085	38.855	18.925	20.00
721	ARG	1HH2	41.874	36.942	20.748	20.00
722	ARG	2HH2	42.724	37.024	22.270	20.00
723	TYR	N	50.170	37.367	19.339	12.06
724	TYR	CA	51.144	38.065	18.550	10.98
725	TYR	C	52.522	37.481	18.816	13.59
726	TYR	O	52.966	37.428	19.960	15.53
727	TYR	CB	51.220	39.576	18.875	9.94
728	TYR	CG	49.859	40.250	18.678	11.54
729	TYR	CD1	49.044	40.145	17.523	11.75
730	TYR	CD2	49.380	40.989	19.752	10.70
731	TYR	CE1	47.808	40.784	17.473	12.58
732	TYR	CE2	48.142	41.590	19.752	11.42
733	TYR	CZ	47.339	41.494	18.578	12.61
734	TYR	OH	46.051	41.986	18.423	13.20
735	TYR	H	50.266	37.312	20.329	20.00
736	TYR	HA	50.862	37.907	17.513	20.00
737	TYR	1HB	51.984	40.094	18.317	20.00
738	TYR	2HB	51.550	39.711	19.903	20.00
739	TYR	HD1	49.336	39.506	16.724	20.00
740	TYR	HD2	49.993	41.106	20.635	20.00
741	TYR	HE1	47.172	40.704	16.611	20.00
742	TYR	HE2	48.011	42.008	20.763	20.00
743	TYR	HH	45.857	42.735	18.985	20.00
744	ARG	N	53.153	37.103	17.699	13.40
745	ARG	CA	54.543	36.623	17.580	16.28
746	ARG	C	55.474	37.666	18.247	14.00
747	ARG	O	56.454	37.285	18.895	16.44
748	ARG	CB	54.915	36.428	16.068	17.48
749	ARG	CG	56.305	36.675	15.419	23.38
750	ARG	CD	56.316	37.199	13.926	28.56
751	ARG	NE	55.326	36.527	13.052	32.94
752	ARG	CZ	54.135	36.980	12.495	34.20
753	ARG	NH1	53.971	38.258	12.223	33.15
754	ARG	NH2	53.182	36.079	12.237	33.58
755	ARG	H	52.559	37.155	16.908	20.00
756	ARG	HA	54.579	35.718	18.147	20.00
757	ARG	1HB	54.506	35.533	15.621	20.00
758	ARG	2HB	54.611	37.441	15.734	20.00
759	ARG	1HG	56.835	37.432	16.015	20.00
760	ARG	2HG	56.937	35.799	15.540	20.00
761	ARG	1HD	56.210	38.289	13.888	20.00
762	ARG	2HD	57.315	36.970	13.512	20.00
763	ARG	HE	55.560	35.563	12.998	20.00
764	ARG	1HH2	52.331	36.288	11.752	20.00
765	ARG	2HH2	53.301	35.150	12.559	20.00
766	ARG	1HH1	53.238	38.710	11.709	20.00
767	ARG	2HH1	54.784	38.793	12.502	20.00
768	ASP	N	55.116	38.934	18.094	12.94
769	ASP	CA	55.973	40.036	18.616	12.52
770	ASP	C	55.797	40.445	20.096	12.63

771	ASP	O	56.452	41.331	20.648	11.75
772	ASP	CB	55.837	41.278	17.706	13.44
773	ASP	CG	56.220	41.009	16.226	15.48
774	ASP	OD1	57.040	40.145	15.911	14.91
775	ASP	OD2	55.608	41.579	15.347	17.68
776	ASP	H	54.485	39.225	17.376	20.00
777	ASP	HA	56.988	39.663	18.528	20.00
778	ASP	1HB	56.501	42.075	18.023	20.00
779	ASP	2HB	54.831	41.662	17.752	20.00
780	VAL	N	54.876	39.733	20.803	12.12
781	VAL	CA	54.573	40.057	22.191	11.29
782	VAL	C	54.455	38.762	22.960	9.78
783	VAL	O	53.550	37.945	22.857	11.48
784	VAL	CB	53.595	41.270	22.522	16.11
785	VAL	CG1	52.686	41.008	23.691	15.44
786	VAL	CG2	53.024	42.155	21.436	14.33
787	VAL	H	54.326	39.100	20.257	20.00
788	VAL	HA	55.521	40.473	22.533	20.00
789	VAL	HB	54.260	42.006	22.986	20.00
790	VAL	1HG1	53.241	40.703	24.580	20.00
791	VAL	2HG1	51.975	40.213	23.479	20.00
792	VAL	3HG1	52.106	41.885	23.978	20.00
793	VAL	1HG2	52.256	41.649	20.862	20.00
794	VAL	2HG2	53.807	42.481	20.755	20.00
795	VAL	3HG2	52.569	43.058	21.839	20.00
796	SER	N	55.506	38.663	23.758	10.16
797	SER	CA	55.834	37.561	24.654	11.16
798	SER	C	56.196	38.081	26.070	9.64
799	SER	O	56.758	39.170	26.254	11.51
800	SER	CB	57.105	36.786	24.050	10.81
801	SER	OG	56.905	36.279	22.695	12.18
802	SER	H	56.131	39.440	23.769	20.00
803	SER	HA	54.941	36.921	24.712	20.00
804	SER	1HB	57.272	35.928	24.740	20.00
805	SER	2HB	58.081	37.304	24.285	20.00
806	SER	HG	56.412	36.740	21.950	20.00
807	PRO	N	55.880	37.202	27.077	8.67
808	PRO	CA	56.329	37.300	28.414	10.79
809	PRO	C	57.824	36.995	28.517	13.35
810	PRO	O	58.237	35.943	28.085	14.81
811	PRO	CB	55.432	36.259	29.103	10.00
812	PRO	CG	55.263	35.208	28.112	10.77
813	PRO	CD	55.042	36.035	26.923	9.16
814	PRO	HA	56.203	38.308	28.764	20.00
815	PRO	1HB	54.379	36.441	29.197	20.00
816	PRO	2HB	55.825	35.933	30.055	20.00
817	PRO	1HG	56.174	34.610	28.028	20.00
818	PRO	2HG	54.446	34.516	28.338	20.00
819	PRO	1HD	54.004	36.311	26.766	20.00
820	PRO	2HD	55.499	35.527	26.092	20.00
821	PHE	N	58.603	37.926	29.144	13.59
822	PHE	CA	59.917	37.512	29.662	12.71

823	PHE	C	59.764	36.228	30.513	12.31
824	PHE	O	58.819	36.148	31.282	12.68
825	PHE	CB	60.730	38.634	30.385	9.81
826	PHE	CG	60.773	39.907	29.668	10.06
827	PHE	CD1	61.171	39.952	28.332	9.58
828	PHE	CD2	60.557	41.099	30.342	9.41
829	PHE	CE1	61.489	41.196	27.800	10.26
830	PHE	CE2	60.848	42.337	29.786	10.02
831	PHE	CZ	61.354	42.399	28.543	8.64
832	PHE	H	58.157	38.782	29.377	20.00
833	PHE	HA	60.489	37.218	28.782	20.00
834	PHE	1HB	61.767	38.289	30.303	20.00
835	PHE	2HB	60.716	38.738	31.460	20.00
836	PHE	HD1	61.347	39.055	27.761	20.00
837	PHE	HD2	60.194	41.061	31.361	20.00
838	PHE	HE1	61.915	41.252	26.806	20.00
839	PHE	HE2	60.710	43.231	30.370	20.00
840	PHE	HZ	61.689	43.349	28.141	20.00
841	ASP	N	60.707	35.281	30.364	11.62
842	ASP	CA	60.799	34.068	31.244	12.07
843	ASP	C	60.796	34.428	32.811	12.27
844	ASP	O	60.121	33.789	33.631	15.21
845	ASP	CB	62.118	33.232	30.924	13.40
846	ASP	CG	62.097	32.558	29.567	14.25
847	ASP	OD1	60.970	32.119	29.186	15.72
848	ASP	OD2	63.206	32.476	28.952	12.79
849	ASP	H	61.362	35.357	29.624	20.00
850	ASP	HA	59.915	33.471	31.028	20.00
851	ASP	1HB	62.233	32.436	31.648	20.00
852	ASP	2HB	63.005	33.861	31.009	20.00
853	HIS	N	61.645	35.431	33.141	12.16
854	HIS	CA	61.906	35.743	34.515	12.71
855	HIS	C	60.622	36.197	35.245	13.92
856	HIS	O	60.428	35.970	36.418	15.61
857	HIS	CB	63.111	36.710	34.678	12.05
858	HIS	CG	62.763	38.170	34.481	10.80
859	HIS	ND1	62.180	38.950	35.412	11.89
860	HIS	CD2	63.026	38.996	33.393	10.89
861	HIS	CE1	62.091	40.203	34.920	9.38
862	HIS	NE2	62.587	40.256	33.707	11.30
863	HIS	H	62.189	35.808	32.392	20.00
864	HIS	HA	62.205	34.800	34.956	20.00
865	HIS	1HB	63.930	36.436	34.003	20.00
866	HIS	2HB	63.521	36.613	35.682	20.00
867	HIS	HD1	61.951	38.686	36.324	20.00
868	HIS	HD2	63.513	38.693	32.486	20.00
869	HIS	HE1	61.660	41.067	35.402	20.00
870	SER	N	59.723	36.834	34.519	13.43
871	SER	CA	58.552	37.448	35.230	12.13
872	SER	C	57.176	36.863	34.862	12.76
873	SER	O	56.104	37.349	35.336	13.37
874	SER	CB	58.525	38.916	34.846	10.16

875	SER	OG	58.653	39.016	33.381	10.34
876	SER	H	59.957	37.166	33.600	20.00
877	SER	HA	58.674	37.373	36.302	20.00
878	SER	1HB	59.441	39.363	35.292	20.00
879	SER	2HB	57.743	39.503	35.420	20.00
880	SER	HG	57.994	38.636	32.702	20.00
881	ARG	N	57.244	35.805	34.022	11.78
882	ARG	CA	55.939	35.373	33.508	13.97
883	ARG	C	55.153	34.605	34.601	13.85
884	ARG	O	55.744	33.997	35.513	11.86
885	ARG	CB	56.173	34.471	32.280	12.96
886	ARG	CG	56.702	33.069	32.654	13.81
887	ARG	CD	57.016	32.181	31.428	13.20
888	ARG	NE	57.632	30.888	31.874	14.78
889	ARG	CZ	57.094	29.687	32.079	15.00
890	ARG	NH1	55.822	29.488	31.874	11.82
891	ARG	NH2	57.838	28.727	32.565	17.64
892	ARG	H	58.122	35.460	33.703	20.00
893	ARG	HA	55.398	36.266	33.193	20.00
894	ARG	1HB	56.888	34.953	31.615	20.00
895	ARG	2HB	55.248	34.372	31.713	20.00
896	ARG	1HG	55.959	32.540	33.249	20.00
897	ARG	2HG	57.586	33.156	33.285	20.00
898	ARG	1HD	57.745	32.661	30.777	20.00
899	ARG	2HD	56.126	31.982	30.828	20.00
900	ARG	HE	58.614	30.885	32.076	20.00
901	ARG	1HH1	55.444	28.561	32.028	20.00
902	ARG	2HH1	55.229	30.225	31.600	20.00
903	ARG	1HH2	57.363	27.856	32.770	20.00
904	ARG	2HH2	58.819	28.824	32.735	20.00
905	ILE	N	53.823	34.541	34.371	14.21
906	ILE	CA	53.015	33.695	35.241	12.58
907	ILE	C	52.784	32.276	34.706	14.61
908	ILE	O	52.311	31.983	33.572	15.26
909	ILE	CB	51.692	34.404	35.385	13.58
910	ILE	CG1	51.914	35.909	35.670	13.29
911	ILE	CG2	50.687	33.768	36.382	13.64
912	ILE	CD1	51.819	36.312	37.125	13.30
913	ILE	H	53.450	35.070	33.611	20.00
914	ILE	HA	53.491	33.658	36.221	20.00
915	ILE	HB	51.217	34.358	34.405	20.00
916	ILE	1HG1	51.085	36.426	35.186	20.00
917	ILE	2HG1	52.780	36.386	35.222	20.00
918	ILE	1HG2	51.116	33.664	37.379	20.00
919	ILE	2HG2	50.394	32.762	36.074	20.00
920	ILE	3HG2	49.777	34.367	36.452	20.00
921	ILE	1HD1	52.673	35.943	37.695	20.00
922	ILE	2HD1	50.909	35.966	37.616	20.00
923	ILE	3HD1	51.834	37.400	37.195	20.00
924	LYS	N	53.090	31.420	35.677	15.82
925	LYS	CA	52.968	29.984	35.485	15.98
926	LYS	C	51.581	29.539	35.986	17.60

927	LYS	O	51.237	29.849	37.111	19.95
928	LYS	CB	54.154	29.264	36.206	17.28
929	LYS	CG	55.459	30.029	36.021	17.24
930	LYS	CD	56.580	29.154	36.468	22.81
931	LYS	CE	57.923	29.820	36.118	26.05
932	LYS	NZ	59.002	28.881	36.461	31.86
933	LYS	H	53.331	31.776	36.578	20.00
934	LYS	HA	53.041	29.782	34.419	20.00
935	LYS	1HB	54.240	28.241	35.827	20.00
936	LYS	2HB	53.945	29.180	37.272	20.00
937	LYS	1HG	55.449	30.949	36.604	20.00
938	LYS	2HG	55.572	30.305	34.972	20.00
939	LYS	1HD	56.527	28.185	35.965	20.00
940	LYS	2HD	56.506	28.962	37.538	20.00
941	LYS	1HE	58.051	30.780	36.631	20.00
942	LYS	2HE	57.975	30.045	35.049	20.00
943	LYS	1HZ	58.861	27.982	35.937	20.00
944	LYS	2HZ	58.998	28.698	37.481	20.00
945	LYS	3HZ	59.917	29.296	36.191	20.00
946	LEU	N	50.885	28.827	35.063	17.25
947	LEU	CA	49.701	28.023	35.305	18.29
948	LEU	C	50.164	26.889	36.218	20.34
949	LEU	O	51.156	26.241	35.911	19.70
950	LEU	CB	49.199	27.455	33.986	18.28
951	LEU	CG	48.053	28.245	33.290	18.66
952	LEU	CD1	47.989	27.995	31.755	17.13
953	LEU	CD2	47.828	29.708	33.707	14.98
954	LEU	H	51.364	28.759	34.195	20.00
955	LEU	HA	48.963	28.629	35.838	20.00
956	LEU	1HB	48.868	26.443	34.106	20.00
957	LEU	2HB	50.029	27.419	33.293	20.00
958	LEU	HG	47.157	27.754	33.671	20.00
959	LEU	1HD1	48.064	26.933	31.522	20.00
960	LEU	2HD1	48.811	28.517	31.259	20.00
961	LEU	3HD1	47.039	28.334	31.374	20.00
962	LEU	1HD2	48.762	30.260	33.691	20.00
963	LEU	2HD2	47.441	29.754	34.725	20.00
964	LEU	3HD2	47.112	30.213	33.062	20.00
965	HIS	N	49.467	26.676	37.346	22.86
966	HIS	CA	49.798	25.580	38.220	25.86
967	HIS	C	49.188	24.299	37.604	30.06
968	HIS	O	48.407	23.576	38.179	31.82
969	HIS	CB	49.207	25.838	39.607	26.12
970	HIS	CG	49.625	27.147	40.252	25.12
971	HIS	ND1	48.983	27.623	41.360	25.76
972	HIS	CD2	50.620	28.085	39.869	24.91
973	HIS	CE1	49.574	28.827	41.642	25.52
974	HIS	NE2	50.566	29.138	40.757	26.33
975	HIS	H	48.586	27.148	37.402	20.00
976	HIS	HA	50.880	25.472	38.282	20.00
977	HIS	1HB	49.461	25.018	40.278	20.00
978	HIS	2HB	48.122	25.837	39.553	20.00

979	HIS	HD1	48.204	27.201	41.765	20.00
980	HIS	HD2	51.269	27.996	39.010	20.00
981	HIS	HE1	49.292	29.465	42.470	20.00
982	GLN	N	49.608	23.987	36.392	32.94
983	GLN	CA	49.271	22.663	35.842	36.50
984	GLN	C	50.532	21.955	35.351	37.97
985	GLN	O	51.618	22.541	35.302	37.18
986	GLN	CB	48.147	22.806	34.854	37.95
987	GLN	CG	48.266	24.086	34.021	40.06
988	GLN	CD	47.360	23.885	32.822	44.06
989	GLN	OE1	47.592	22.903	32.119	46.49
990	GLN	NE2	46.323	24.719	32.620	41.49
991	GLN	H	50.243	24.612	35.941	20.00
992	GLN	HA	48.926	21.997	36.641	20.00
993	GLN	1HB	47.226	22.901	35.438	20.00
994	GLN	2HB	48.003	21.889	34.282	20.00
995	GLN	1HG	49.283	24.268	33.676	20.00
996	GLN	2HG	47.866	24.901	34.612	20.00
997	GLN	1HE2	45.658	24.510	31.912	20.00
998	GLN	2HE2	46.171	25.495	33.241	20.00
999	GLU	N	50.320	20.649	35.092	41.15
1000	GLU	CA	51.547	19.859	34.850	41.70
1001	GLU	C	51.834	19.728	33.311	39.31
1002	GLU	O	52.984	19.644	32.860	38.68
1003	GLU	CB	51.430	18.558	35.655	45.57
1004	GLU	CG	51.679	18.866	37.145	54.22
1005	GLU	CD	50.777	17.977	38.035	60.23
1006	GLU	OE1	49.587	18.325	38.117	63.36
1007	GLU	OE2	51.253	16.964	38.605	62.48
1008	GLU	H	49.451	20.221	35.343	20.00
1009	GLU	HA	52.415	20.380	35.254	20.00
1010	GLU	1HB	52.138	17.803	35.321	20.00
1011	GLU	2HB	50.436	18.128	35.508	20.00
1012	GLU	1HG	51.411	19.888	37.403	20.00
1013	GLU	2HG	52.719	18.720	37.428	20.00
1014	ASP	N	50.713	19.782	32.532	38.53
1015	ASP	CA	50.859	19.700	31.061	37.73
1016	ASP	C	51.793	20.877	30.583	33.50
1017	ASP	O	52.946	20.793	30.147	35.46
1018	ASP	CB	49.374	19.842	30.492	43.21
1019	ASP	CG	49.448	20.048	28.963	49.96
1020	ASP	OD1	50.358	19.411	28.396	53.55
1021	ASP	OD2	48.668	20.859	28.386	52.89
1022	ASP	H	49.807	19.888	32.924	20.00
1023	ASP	HA	51.321	18.751	30.761	20.00
1024	ASP	1HB	48.803	20.635	30.964	20.00
1025	ASP	2HB	48.830	18.915	30.646	20.00
1026	ASN	N	51.117	22.012	30.774	28.37
1027	ASN	CA	51.658	23.198	30.253	21.99
1028	ASN	C	51.272	24.281	31.204	20.24
1029	ASN	O	50.088	24.519	31.310	21.87
1030	ASN	CB	51.062	23.311	28.867	19.04

1031	ASN	CG	51.901	24.202	27.972	18.04
1032	ASN	OD1	52.747	24.954	28.409	19.25
1033	ASN	ND2	51.670	24.083	26.677	15.06
1034	ASN	H	50.148	21.879	30.992	20.00
1035	ASN	HA	52.742	23.147	30.225	20.00
1036	ASN	1HB	50.053	23.709	28.917	20.00
1037	ASN	2HB	50.976	22.339	28.367	20.00
1038	ASN	1HD2	52.136	24.800	26.133	20.00
1039	ASN	2HD2	51.105	23.357	26.296	20.00
1040	ASP	N	52.310	24.934	31.781	18.00
1041	ASP	CA	52.359	26.033	32.774	18.78
1042	ASP	C	52.269	27.339	32.022	17.35
1043	ASP	O	52.385	28.381	32.643	18.81
1044	ASP	CB	53.678	26.048	33.673	19.48
1045	ASP	CG	55.010	26.577	33.066	23.10
1046	ASP	OD1	55.075	26.798	31.865	24.35
1047	ASP	OD2	56.022	26.809	33.756	29.58
1048	ASP	H	53.213	24.652	31.479	20.00
1049	ASP	HA	51.485	25.929	33.416	20.00
1050	ASP	1HB	53.905	25.042	34.027	20.00
1051	ASP	2HB	53.466	26.618	34.583	20.00
1052	TYR	N	52.126	27.268	30.658	16.55
1053	TYR	CA	52.342	28.547	29.854	12.98
1054	TYR	C	51.059	29.382	29.617	12.27
1055	TYR	O	50.072	28.908	29.056	12.81
1056	TYR	CB	53.128	28.308	28.524	10.36
1057	TYR	CG	53.307	29.633	27.752	12.42
1058	TYR	CD1	54.305	30.529	28.104	10.55
1059	TYR	CD2	52.385	30.073	26.782	11.80
1060	TYR	CE1	54.386	31.783	27.545	11.79
1061	TYR	CE2	52.453	31.353	26.260	10.71
1062	TYR	CZ	53.524	32.198	26.591	9.67
1063	TYR	OH	53.938	33.401	26.004	10.99
1064	TYR	H	52.132	26.366	30.228	20.00
1065	TYR	HA	53.022	29.162	30.449	20.00
1066	TYR	1HB	52.598	27.575	27.914	20.00
1067	TYR	2HB	54.096	27.862	28.732	20.00
1068	TYR	HD1	55.008	30.232	28.857	20.00
1069	TYR	HD2	51.588	29.416	26.475	20.00
1070	TYR	HE1	55.198	32.442	27.833	20.00
1071	TYR	HE2	51.561	31.484	25.630	20.00
1072	TYR	HH	53.565	33.505	25.119	20.00
1073	ILE	N	51.111	30.653	30.018	13.06
1074	ILE	CA	50.146	31.725	29.683	12.41
1075	ILE	C	50.996	32.948	29.283	11.32
1076	ILE	O	52.043	33.149	29.862	12.19
1077	ILE	CB	49.059	32.003	30.788	12.98
1078	ILE	CG1	48.065	33.056	30.196	8.76
1079	ILE	CG2	49.639	32.315	32.217	10.91
1080	ILE	CD1	46.906	33.342	31.116	9.88
1081	ILE	H	51.869	30.910	30.612	20.00
1082	ILE	HA	49.636	31.400	28.775	20.00

1083	ILE	HB	48.500	31.076	30.889	20.00
1084	ILE	1HG1	47.659	32.732	29.240	20.00
1085	ILE	2HG1	48.584	33.993	30.018	20.00
1086	ILE	1HG2	50.271	33.197	32.211	20.00
1087	ILE	2HG2	50.242	31.487	32.577	20.00
1088	ILE	3HG2	48.844	32.475	32.935	20.00
1089	ILE	1HD1	47.243	33.841	32.021	20.00
1090	ILE	2HD1	46.420	32.423	31.431	20.00
1091	ILE	3HD1	46.150	33.978	30.654	20.00
1092	ASN	N	50.614	33.705	28.262	9.16
1093	ASN	CA	51.251	34.994	27.951	9.65
1094	ASN	C	50.836	36.013	28.977	10.37
1095	ASN	O	49.889	36.738	28.762	10.07
1096	ASN	CB	50.740	35.386	26.534	9.08
1097	ASN	CG	51.559	36.512	25.985	9.54
1098	ASN	OD1	51.733,	37.578	26.614	10.96
1099	ASN	ND2	52.102	36.212	24.777	9.06
1100	ASN	H	49.891	33.381	27.666	20.00
1101	ASN	HA	52.326	34.865	28.001	20.00
1102	ASN	1HB	49.721	35.743	26.595	20.00
1103	ASN	2HB	50.681	34.548	25.844	20.00
1104	ASN	1HD2	52.677	36.857	24.276	20.00
1105	ASN	2HD2	51.947	35.294	24.398	20.00
1106	ALA	N	51.472	36.004	30.161	9.41
1107	ALA	CA	51.160	37.001	31.204	10.05
1108	ALA	C	52.418	37.231	31.951	11.58
1109	ALA	O	53.203	36.292	32.110	12.92
1110	ALA	CB	50.197	36.373	32.229	7.50
1111	ALA	H	52.104	35.256	30.340	20.00
1112	ALA	HA	50.721	37.888	30.752	20.00
1113	ALA	1HB	50.631	35.477	32.665	20.00
1114	ALA	2HB	49.277	36.060	31.754	20.00
1115	ALA	3HB	49.933	37.050	33.037	20.00
1116	SER	N	52.522	38.468	32.470	10.51
1117	SER	CA	53.663	38.902	33.299	11.23
1118	SER	C	53.285	39.621	34.550	10.85
1119	SER	O	52.423	40.474	34.557	12.48
1120	SER	CB	54.393	39.958	32.386	7.55
1121	SER	OG	54.544	39.424	30.979	10.45
1122	SER	H	51.738	39.068	32.307	20.00
1123	SER	HA	54.292	38.048	33.555	20.00
1124	SER	1HB	55.364	40.197	32.840	20.00
1125	SER	2HB	53.966	41.002	32.539	20.00
1126	SER	HG	53.779	38.963	30.539	20.00
1127	LEU	N	54.089	39.317	35.577	11.48
1128	LEU	CA	53.997	40.074	36.831	12.53
1129	LEU	C	54.875	41.328	36.773	13.15
1130	LEU	O	56.106	41.237	36.710	13.65
1131	LEU	CB	54.509	39.118	37.938	13.18
1132	LEU	CG	54.050	39.236	39.386	15.58
1133	LEU	CD1	53.078	40.321	39.819	15.45
1134	LEU	CD2	55.183	39.160	40.327	15.90

1135	LEU	H	54.798	38.633	35.444	20.00
1136	LEU	HA	52.955	40.335	37.005	20.00
1137	LEU	1HB	55.596	39.023	37.872	20.00
1138	LEU	2HB	54.181	38.124	37.632	20.00
1139	LEU	HG	53.486	38.316	39.575	20.00
1140	LEU	1HD1	52.149	40.243	39.258	20.00
1141	LEU	2HD1	53.486	41.319	39.654	20.00
1142	LEU	3HD1	52.812	40.238	40.873	20.00
1143	LEU	1HD2	55.856	39.996	40.139	20.00
1144	LEU	2HD2	55.743	38.233	40.214	20.00
1145	LEU	3HD2	54.838	39.213	41.361	20.00
1146	ILE	N	54.198	42.491	36.870	12.91
1147	ILE	CA	54.849	43.764	37.188	13.87
1148	ILE	C	54.768	44.035	38.703	16.47
1149	ILE	O	53.759	44.202	39.394	16.73
1150	ILE	CB	54.282	44.944	36.382	13.55
1151	ILE	CG1	54.385	44.786	34.837	12.82
1152	ILE	CG2	54.940	46.250	36.798	16.67
1153	ILE	CD1	54.103	43.394	34.279	12.75
1154	ILE	H	53.200	42.393	36.826	20.00
1155	ILE	HA	55.895	43.661	36.897	20.00
1156	ILE	HB	53.217	45.012	36.617	20.00
1157	ILE	1HG1	55.383	45.077	34.511	20.00
1158	ILE	2HG1	53.700	45.497	34.362	20.00
1159	ILE	1HG2	56.026	46.220	36.689	20.00
1160	ILE	2HG2	54.753	46.467	37.845	20.00
1161	ILE	3HG2	54.556	47.094	36.229	20.00
1162	ILE	1HD1	53.156	42.977	34.619	20.00
1163	ILE	2HD1	54.904	42.685	34.471	20.00
1164	ILE	3HD1	54.016	43.465	33.195	20.00
1165	LYS	N	55.961	44.052	39.204	16.38
1166	LYS	CA	56.155	44.186	40.594	19.03
1167	LYS	C	56.848	45.516	40.860	18.79
1168	LYS	O	58.065	45.591	40.884	18.39
1169	LYS	CB	56.939	42.956	40.929	24.89
1170	LYS	CG	56.912	42.866	42.439	36.70
1171	LYS	CD	57.328	41.533	43.051	45.35
1172	LYS	CE	57.186	41.692	44.560	49.89
1173	LYS	NZ	57.538	40.467	45.290	53.29
1174	LYS	H	56.745	43.962	38.586	20.00
1175	LYS	HA	55.199	44.202	41.123	20.00
1176	LYS	1HB	57.961	43.013	40.539	20.00
1177	LYS	2HB	56.467	42.081	40.482	20.00
1178	LYS	1HG	55.910	43.036	42.726	20.00
1179	LYS	2HG	57.473	43.692	42.872	20.00
1180	LYS	1HD	58.364	41.333	42.777	20.00
1181	LYS	2HD	56.711	40.725	42.648	20.00
1182	LYS	1HE	56.135	41.919	44.779	20.00
1183	LYS	2HE	57.770	42.540	44.932	20.00
1184	LYS	1HZ	58.555	40.282	45.176	20.00
1185	LYS	2HZ	57.015	39.665	44.873	20.00
1186	LYS	3HZ	57.314	40.520	46.304	20.00

1187	MET	N	56.027	46.567	41.062	17.44
1188	MET	CA	56.634	47.846	41.393	17.07
1189	MET	C	57.007	47.929	42.923	17.04
1190	MET	O	56.147	48.095	43.790	16.87
1191	MET	CB	55.675	48.907	40.957	15.46
1192	MET	CG	55.291	48.734	39.503	15.47
1193	MET	SD	56.753	48.529	38.450	16.71
1194	MET	CE	57.080	50.195	38.026	12.89
1195	MET	H	55.032	46.464	41.035	20.00
1196	MET	HA	57.546	47.951	40.808	20.00
1197	MET	1HB	56.133	49.884	41.087	20.00
1198	MET	2HB	54.772	48.927	41.568	20.00
1199	MET	1HG	54.709	49.588	39.160	20.00
1200	MET	2HG	54.618	47.892	39.385	20.00
1201	MET	1HE	57.389	50.721	38.923	20.00
1202	MET	2HE	56.172	50.653	37.664	20.00
1203	MET	3HE	57.869	50.255	37.283	20.00
1204	GLU	N	58.311	47.763	43.214	20.27
1205	GLU	CA	58.778	47.729	44.589	22.54
1206	GLU	C	58.455	49.032	45.367	22.33
1207	GLU	O	57.551	49.145	46.174	24.08
1208	GLU	CB	60.261	47.369	44.550	26.36
1209	GLU	CG	60.752	46.542	45.777	35.25
1210	GLU	CD	62.306	46.400	45.765	40.00
1211	GLU	OE1	63.007	47.377	46.070	43.15
1212	GLU	OE2	62.798	45.322	45.423	43.54
1213	GLU	H	58.846	47.524	42.399	20.00
1214	GLU	HA	58.235	46.912	45.065	20.00
1215	GLU	1HB	60.894	48.246	44.415	20.00
1216	GLU	2HB	60.457	46.747	43.675	20.00
1217	GLU	1HG	60.308	45.548	45.809	20.00
1218	GLU	2HG	60.494	47.045	46.708	20.00
1219	GLU	N	59.176	50.055	45.053	23.41
1220	GLU	CA	58.964	51.347	45.670	24.81
1221	GLU	C	57.479	51.755	45.865	24.74
1222	GLU	O	57.051	52.142	46.947	24.77
1223	GLU	CB	59.765	52.321	44.797	26.99
1224	GLU	CG	59.810	53.801	45.255	35.79
1225	GLU	CD	60.222	54.688	44.049	45.06
1226	GLU	OE1	59.969	54.335	42.876	48.32
1227	GLU	OE2	60.747	55.769	44.308	49.68
1228	GLU	H	59.978	49.853	44.499	20.00
1229	GLU	HA	59.422	51.306	46.657	20.00
1230	GLU	1HB	59.378	52.294	43.798	20.00
1231	GLU	2HB	60.779	51.944	44.681	20.00
1232	GLU	1HG	60.583	53.892	46.009	20.00
1233	GLU	2HG	58.858	54.133	45.660	20.00
1234	ALA	N	56.670	51.652	44.799	22.17
1235	ALA	CA	55.246	52.057	44.836	21.64
1236	ALA	C	54.359	51.006	45.549	22.46
1237	ALA	O	53.160	51.123	45.691	24.05
1238	ALA	CB	54.806	52.202	43.399	20.53

1239	ALA	H	57.053	51.248	43.967	20.00
1240	ALA	HA	55.174	53.008	45.366	20.00
1241	ALA	1HB	54.756	51.228	42.929	20.00
1242	ALA	2HB	55.522	52.775	42.815	20.00
1243	ALA	3HB	53.829	52.664	43.317	20.00
1244	GLN	N	55.030	49.944	45.995	23.74
1245	GLN	CA	54.391	48.860	46.644	27.80
1246	GLN	C	53.125	48.391	45.853	26.92
1247	GLN	O	52.149	47.989	46.495	27.71
1248	GLN	CB	54.140	49.267	48.138	32.88
1249	GLN	CG	55.326	49.006	49.110	40.36
1250	GLN	CD	55.212	47.532	49.760	47.19
1251	GLN	OE1	54.421	47.292	50.673	52.84
1252	GLN	NE2	56.012	46.546	49.265	46.59
1253	GLN	H	55.964	49.826	45.665	20.00
1254	GLN	HA	55.085	48.022	46.580	20.00
1255	GLN	1HB	53.282	48.717	48.513	20.00
1256	GLN	2HB	53.816	50.302	48.171	20.00
1257	GLN	1HG	55.368	49.735	49.918	20.00
1258	GLN	2HG	56.264	49.080	48.553	20.00
1259	GLN	1HE2	55.903	45.690	49.757	20.00
1260	GLN	2HE2	56.637	46.689	48.503	20.00
1261	ARG	N	53.166	48.361	44.464	23.43
1262	ARG	CA	52.057	47.713	43.751	18.91
1263	ARG	C	52.453	46.726	42.694	16.84
1264	ARG	O	53.318	47.057	41.916	17.96
1265	ARG	CB	51.320	48.807	43.076	18.58
1266	ARG	CG	50.098	48.257	42.395	16.36
1267	ARG	CD	49.034	49.322	42.305	17.70
1268	ARG	NE	48.208	49.346	43.527	17.29
1269	ARG	CZ	47.441	50.424	43.806	15.94
1270	ARG	NH1	47.297	51.403	42.891	13.68
1271	ARG	NH2	46.819	50.417	44.975	18.40
1272	ARG	H	54.018	48.616	44.002	20.00
1273	ARG	HA	51.427	47.185	44.462	20.00
1274	ARG	1HB	51.976	49.317	42.372	20.00
1275	ARG	2HB	51.053	49.558	43.825	20.00
1276	ARG	1HG	49.683	47.403	42.929	20.00
1277	ARG	2HG	50.353	47.899	41.397	20.00
1278	ARG	1HD	48.372	49.152	41.452	20.00
1279	ARG	2HD	49.446	50.319	42.247	20.00
1280	ARG	HE	48.258	48.588	44.171	20.00
1281	ARG	1HH1	46.755	52.223	43.004	20.00
1282	ARG	2HH1	47.752	51.289	41.992	20.00
1283	ARG	1HH2	46.269	51.202	45.245	20.00
1284	ARG	2HH2	46.898	49.595	45.539	20.00
1285	SER	N	51.766	45.572	42.683	13.82
1286	SER	CA	51.692	44.596	41.633	12.48
1287	SER	C	50.434	44.551	40.727	11.37
1288	SER	O	49.287	44.615	41.157	13.16
1289	SER	CB	51.817	43.113	42.100	12.86
1290	SER	OG	53.028	42.834	42.899	19.01

1291	SER	H	51.167	45.419	43.464	20.00
1292	SER	HA	52.523	44.871	41.005	20.00
1293	SER	1HB	51.950	42.559	41.136	20.00
1294	SER	2HB	50.804	42.672	42.377	20.00
1295	SER	HG	53.168	43.269	43.803	20.00
1296	TYR	N	50.787	44.235	39.430	11.99
1297	TYR	CA	49.732	44.002	38.418	10.12
1298	TYR	C	50.149	42.759	37.675	10.62
1299	TYR	O	51.329	42.534	37.602	11.32
1300	TYR	CB	49.562	45.151	37.368	10.39
1301	TYR	CG	49.764	46.542	37.950	10.08
1302	TYR	CD1	51.063	46.952	38.255	10.55
1303	TYR	CD2	48.695	47.416	38.159	10.53
1304	TYR	CE1	51.305	48.211	38.707	12.90
1305	TYR	CE2	48.895	48.689	38.649	12.10
1306	TYR	CZ	50.180	49.106	38.885	13.13
1307	TYR	OH	50.199	50.433	39.253	13.22
1308	TYR	H	51.751	44.131	39.179	20.00
1309	TYR	HA	48.782	43.799	38.924	20.00
1310	TYR	1HB	48.582	45.095	36.888	20.00
1311	TYR	2HB	50.285	45.040	36.555	20.00
1312	TYR	HD1	51.873	46.248	38.135	20.00
1313	TYR	HD2	47.680	47.117	37.910	20.00
1314	TYR	HE1	52.383	48.243	38.882	20.00
1315	TYR	HE2	48.058	49.352	38.782	20.00
1316	TYR	HH	50.979	50.728	39.691	20.00
1317	ILE	N	49.222	42.018	37.068	10.35
1318	ILE	CA	49.503	41.053	35.972	7.97
1319	ILE	C	49.087	41.676	34.586	9.78
1320	ILE	O	47.914	41.999	34.387	10.25
1321	ILE	CB	48.760	39.736	36.289	9.05
1322	ILE	CG1	49.269	39.172	37.681	10.20
1323	ILE	CG2	48.976	38.754	35.095	8.37
1324	ILE	CD1	48.737	37.834	38.236	8.33
1325	ILE	H	48.275	42.270	37.213	20.00
1326	ILE	HA	50.572	40.865	35.958	20.00
1327	ILE	HB	47.694	39.953	36.380	20.00
1328	ILE	1HG1	49.048	39.919	38.429	20.00
1329	ILE	2HG1	50.359	39.121	37.645	20.00
1330	ILE	1HG2	50.043	38.615	34.936	20.00
1331	ILE	2HG2	48.543	39.117	34.167	20.00
1332	ILE	3HG2	48.537	37.783	35.302	20.00
1333	ILE	1HD1	49.021	37.050	37.542	20.00
1334	ILE	2HD1	47.661	37.804	38.225	20.00
1335	ILE	3HD1	49.128	37.549	39.212	20.00
1336	LEU	N	50.086	41.866	33.670	8.73
1337	LEU	CA	49.787	42.333	32.269	8.66
1338	LEU	C	49.661	41.053	31.404	11.10
1339	LEU	O	50.565	40.223	31.418	12.49
1340	LEU	CB	50.852	43.343	31.645	9.65
1341	LEU	CG	50.557	44.804	32.004	10.58
1342	LEU	CD1	51.628	45.857	31.638	11.19

1343	LEU	CD2	50.324	44.924	33.515	12.47
1344	LEU	H	50.995	41.592	33.979	20.00
1345	LEU	HA	48.813	42.831	32.284	20.00
1346	LEU	1HB	50.867	43.235	30.561	20.00
1347	LEU	2HB	51.845	43.080	32.000	20.00
1348	LEU	HG	49.634	45.070	31.499	20.00
1349	LEU	1HD1	51.749	45.864	30.559	20.00
1350	LEU	2HD1	52.586	45.584	32.073	20.00
1351	LEU	3HD1	51.364	46.862	31.958	20.00
1352	LEU	1HD2	51.193	44.547	34.051	20.00
1353	LEU	2HD2	49.440	44.385	33.853	20.00
1354	LEU	3HD2	50.173	45.958	33.809	20.00
1355	THR	N	48.531	40.850	30.708	10.83
1356	THR	CA	48.266	39.641	29.888	8.06
1357	THR	C	47.699	40.039	28.466	9.10
1358	THR	O	47.222	41.124	28.225	8.53
1359	THR	CB	47.333	38.650	30.660	8.87
1360	THR	OG1	47.456	37.292	30.225	11.27
1361	THR	CG2	45.834	39.019	30.813	8.63
1362	THR	H	47.838	41.569	30.829	20.00
1363	THR	HA	49.265	39.242	29.728	20.00
1364	THR	HB	47.726	38.689	31.711	20.00
1365	THR	HG1	47.258	36.919	29.323	20.00
1366	THR	1HG2	45.238	39.174	29.907	20.00
1367	THR	2HG2	45.766	39.973	31.337	20.00
1368	THR	3HG2	45.335	38.315	31.484	20.00
1369	GLN	N	47.760	39.180	27.461	7.55
1370	GLN	CA	47.071	39.610	26.199	7.51
1371	GLN	C	45.534	39.436	26.344	8.15
1372	GLN	O	45.108	38.664	27.188	9.26
1373	GLN	CB	47.562	38.744	25.030	7.72
1374	GLN	CG	47.407	37.252	25.399	7.48
1375	GLN	CD	47.989	36.233	24.490	7.54
1376	GLN	OE1	47.581	35.092	24.452	13.65
1377	GLN	NE2	49.116	36.537	23.918	6.16
1378	GLN	H	48.093	38.257	27.639	20.00
1379	GLN	HA	47.281	40.663	25.990	20.00
1380	GLN	1HB	48.615	38.974	24.855	20.00
1381	GLN	2HB	47.022	38.964	24.104	20.00
1382	GLN	1HG	46.374	36.962	25.596	20.00
1383	GLN	2HG	47.973	37.052	26.297	20.00
1384	GLN	1HE2	49.523	35.662	23.730	20.00
1385	GLN	2HE2	49.492	37.437	23.695	20.00
1386	GLY	N	44.700	40.048	25.468	8.70
1387	GLY	CA	43.381	39.512	25.333	8.95
1388	GLY	C	43.447	37.969	25.067	10.89
1389	GLY	O	44.117	37.488	24.141	12.56
1390	GLY	H	45.110	40.695	24.840	20.00
1391	GLY	1HA	42.923	40.000	24.471	20.00
1392	GLY	2HA	42.825	39.769	26.226	20.00
1393	PRO	N	42.703	37.161	25.868	11.90
1394	PRO	CA	42.702	35.712	25.665	10.45

1395	PRO	C	42.336	35.222	24.206	12.59
1396	PRO	O	41.485	35.804	23.503	12.30
1397	PRO	CB	41.616	35.253	26.615	10.51
1398	PRO	CG	41.508	36.340	27.662	11.89
1399	PRO	CD	41.846	37.636	26.938	9.07
1400	PRO	HA	43.706	35.498	26.026	20.00
1401	PRO	1HB	41.830	34.304	27.113	20.00
1402	PRO	2HB	40.642	35.140	26.128	20.00
1403	PRO	1HG	40.578	36.362	28.234	20.00
1404	PRO	2HG	42.309	36.169	28.380	20.00
1405	PRO	1HD	42.340	38.326	27.629	20.00
1406	PRO	2HD	40.938	38.092	26.560	20.00
1407	LEU	N	42.979	34.139	23.738	13.19
1408	LEU	CA	42.570	33.451	22.471	14.02
1409	LEU	C	41.455	32.441	22.773	13.93
1410	LEU	O	41.173	32.179	23.932	12.95
1411	LEU	CB	43.705	32.668	21.783	13.39
1412	LEU	CG	44.875	33.411	21.125	14.69
1413	LEU	CD1	46.091	33.381	21.981	13.28
1414	LEU	CD2	44.589	34.682	20.356	12.21
1415	LEU	H	43.863	33.945	24.174	20.00
1416	LEU	HA	42.170	34.195	21.784	20.00
1417	LEU	1HB	43.310	32.178	20.906	20.00
1418	LEU	2HB	44.080	31.757	22.250	20.00
1419	LEU	HG	45.188	32.734	20.321	20.00
1420	LEU	1HD1	46.300	32.381	22.362	20.00
1421	LEU	2HD1	46.027	34.045	22.844	20.00
1422	LEU	3HD1	46.952	33.682	21.388	20.00
1423	LEU	1HD2	44.522	35.528	21.034	20.00
1424	LEU	2HD2	43.657	34.594	19.801	20.00
1425	LEU	3HD2	45.373	34.903	19.634	20.00
1426	PRO	N	40.810	31.845	21.721	16.81
1427	PRO	CA	39.625	31.072	21.951	17.34
1428	PRO	C	39.955	29.842	22.707	16.85
1429	PRO	O	39.063	29.280	23.267	18.24
1430	PRO	CB	39.185	30.662	20.513	17.12
1431	PRO	CG	39.775	31.705	19.619	19.47
1432	PRO	CD	41.112	31.934	20.286	16.45
1433	PRO	HA	38.865	31.652	22.479	20.00
1434	PRO	1HB	38.100	30.601	20.422	20.00
1435	PRO	2HB	39.579	29.685	20.211	20.00
1436	PRO	1HG	39.869	31.368	18.588	20.00
1437	PRO	2HG	39.170	32.614	19.648	20.00
1438	PRO	1HD	41.526	32.906	20.005	20.00
1439	PRO	2HD	41.807	31.143	19.988	20.00
1440	ASN	N	41.232	29.451	22.729	15.30
1441	ASN	CA	41.785	28.298	23.484	14.86
1442	ASN	C	42.556	28.687	24.770	15.36
1443	ASN	O	43.108	27.833	25.417	15.84
1444	ASN	CB	42.877	27.529	22.617	14.48
1445	ASN	CG	44.147	28.314	22.038	16.03
1446	ASN	OD1	44.043	29.255	21.263	19.68

1447	ASN	ND2	45.329	27.892	22.449	15.67
1448	ASN	H	41.818	29.895	22.060	20.00
1449	ASN	HA	40.954	27.643	23.757	20.00
1450	ASN	1HB	42.375	27.105	21.737	20.00
1451	ASN	2HB	43.249	26.672	23.187	20.00
1452	ASN	1HD2	46.001	28.521	22.054	20.00
1453	ASN	2HD2	45.568	27.139	23.052	20.00
1454	THR	N	42.650	29.978	25.133	15.02
1455	THR	CA	43.391	30.291	26.417	12.29
1456	THR	C	42.474	31.036	27.517	11.96
1457	THR	O	42.852	31.476	28.583	11.69
1458	THR	CB	44.719	31.008	26.014	10.87
1459	THR	OG1	44.565	32.343	25.555	10.92
1460	THR	CG2	45.584	30.273	25.027	10.49
1461	THR	H	42.262	30.664	24.515	20.00
1462	THR	HA	43.646	29.369	26.917	20.00
1463	THR	HB	45.361	30.992	26.941	20.00
1464	THR	HG1	43.754	32.671	25.107	20.00
1465	THR	1HG2	45.153	30.085	24.039	20.00
1466	THR	2HG2	45.915	29.312	25.408	20.00
1467	THR	3HG2	46.499	30.848	24.857	20.00
1468	CYS	N	41.161	31.075	27.244	14.04
1469	CYS	CA	40.171	31.667	28.138	14.17
1470	CYS	C	40.085	30.933	29.493	12.97
1471	CYS	O	39.963	31.492	30.591	13.90
1472	CYS	CB	38.786	31.617	27.536	13.16
1473	CYS	SG	38.550	32.838	26.281	15.24
1474	CYS	H	40.878	30.770	26.336	20.00
1475	CYS	HA	40.460	32.696	28.339	20.00
1476	CYS	1HB	38.031	31.820	28.305	20.00
1477	CYS	2HB	38.541	30.623	27.152	20.00
1478	CYS	HG	38.695	32.291	25.082	20.00
1479	GLY	N	40.243	29.645	29.298	13.25
1480	GLY	CA	40.387	28.785	30.429	14.11
1481	GLY	C	41.808	28.832	31.180	14.77
1482	GLY	O	41.877	28.613	32.340	15.71
1483	GLY	H	40.296	29.275	28.376	20.00
1484	GLY	1HA	40.315	27.866	29.861	20.00
1485	GLY	2HA	39.548	29.026	31.088	20.00
1486	HIS	N	42.939	29.144	30.573	15.04
1487	HIS	CA	44.200	29.473	31.244	13.49
1488	HIS	C	43.971	30.831	31.942	14.38
1489	HIS	O	44.520	31.190	32.974	15.19
1490	HIS	CB	45.303	29.659	30.149	12.89
1491	HIS	CG	45.443	28.449	29.222	14.63
1492	HIS	ND1	45.683	28.487	27.875	13.48
1493	HIS	CD2	45.237	27.096	29.517	16.55
1494	HIS	CE1	45.572	27.255	27.426	14.33
1495	HIS	NE2	45.317	26.382	28.410	15.87
1496	HIS	H	42.914	28.968	29.590	20.00
1497	HIS	HA	44.420	28.687	31.970	20.00
1498	HIS	1HB	46.257	29.992	30.558	20.00

1499	HIS	2HB	44.992	30.483	29.501	20.00
1500	HIS	HD1	45.880	29.274	27.336	20.00
1501	HIS	HD2	44.997	26.700	30.496	20.00
1502	HIS	HE1	45.646	26.975	26.381	20.00
1503	PHE	N	43.159	31.695	31.311	12.72
1504	PHE	CA	43.089	33.072	31.837	12.68
1505	PHE	C	42.415	33.006	33.201	13.22
1506	PHE	O	42.872	33.545	34.203	12.12
1507	PHE	CB	42.315	33.909	30.774	12.82
1508	PHE	CG	42.032	35.335	31.183	9.60
1509	PHE	CD1	40.875	35.627	31.879	8.18
1510	PHE	CD2	42.919	36.384	30.909	8.54
1511	PHE	CE1	40.653	36.859	32.368	11.79
1512	PHE	CE2	42.654	37.665	31.367	11.03
1513	PHE	CZ	41.535	37.845	32.118	10.70
1514	PHE	H	42.743	31.410	30.457	20.00
1515	PHE	HA	44.103	33.467	31.947	20.00
1516	PHE	1HB	41.355	33.453	30.563	20.00
1517	PHE	2HB	42.841	33.912	29.814	20.00
1518	PHE	HD1	40.158	34.849	32.083	20.00
1519	PHE	HD2	43.824	36.183	30.347	20.00
1520	PHE	HE1	39.765	37.060	32.953	20.00
1521	PHE	HE2	43.281	38.521	31.136	20.00
1522	PHE	HZ	41.317	38.835	32.490	20.00
1523	TRP	N	41.278	32.289	33.173	12.17
1524	TRP	CA	40.450	32.222	34.411	12.15
1525	TRP	C	41.113	31.433	35.595	12.77
1526	TRP	O	41.043	31.813	36.756	12.89
1527	TRP	CB	39.015	31.707	34.001	13.28
1528	TRP	CG	38.226	32.858	33.399	13.46
1529	TRP	CD1	37.724	32.964	32.065	13.99
1530	TRP	CD2	37.952	34.113	34.051	12.69
1531	TRP	NE1	37.180	34.195	31.900	13.76
1532	TRP	CE2	37.314	34.931	33.090	12.21
1533	TRP	CE3	38.279	34.589	35.303	11.54
1534	TRP	CZ2	36.958	36.217	33.415	11.49
1535	TRP	CZ3	37.922	35.900	35.617	12.46
1536	TRP	CH2	37.265	36.700	34.699	11.61
1537	TRP	H	40.911	31.965	32.302	20.00
1538	TRP	HA	40.399	33.239	34.783	20.00
1539	TRP	1HB	38.472	31.313	34.862	20.00
1540	TRP	2HB	39.104	30.873	33.295	20.00
1541	TRP	HD1	37.760	32.155	31.345	20.00
1542	TRP	HE1	36.707	34.474	31.085	20.00
1543	TRP	HE3	38.784	33.971	36.026	20.00
1544	TRP	HZ2	36.450	36.835	32.687	20.00
1545	TRP	HZ3	38.094	36.300	36.599	20.00
1546	TRP	HH2	36.986	37.699	34.976	20.00
1547	GLU	N	41.780	30.326	35.178	13.48
1548	GLU	CA	42.730	29.627	35.996	12.78
1549	GLU	C	43.768	30.566	36.534	13.54
1550	GLU	O	43.972	30.594	37.732	13.56

1551	GLU	CB	43.388	28.531	35.219	11.88
1552	GLU	CG	44.436	27.771	36.130	15.11
1553	GLU	CD	45.202	26.754	35.308	17.43
1554	GLU	OE1	44.936	26.639	34.112	19.12
1555	GLU	OE2	46.076	26.069	35.793	19.81
1556	GLU	H	41.624	30.031	34.237	20.00
1557	GLU	HA	42.211	29.204	36.855	20.00
1558	GLU	1HB	43.840	28.925	34.313	20.00
1559	GLU	2HB	42.624	27.820	34.904	20.00
1560	GLU	1HG	43.929	27.252	36.939	20.00
1561	GLU	2HG	45.161	28.434	36.597	20.00
1562	MET	N	44.363	31.442	35.736	11.71
1563	MET	CA	45.348	32.380	36.339	12.23
1564	MET	C	44.716	33.407	37.337	11.68
1565	MET	O	45.324	33.773	38.327	11.24
1566	MET	CB	46.127	33.111	35.218	9.82
1567	MET	CG	46.844	34.402	35.674	11.63
1568	MET	SD	47.623	35.297	34.348	15.04
1569	MET	CE	46.176	36.105	33.568	11.38
1570	MET	H	44.302	31.230	34.763	20.00
1571	MET	HA	46.042	31.771	36.918	20.00
1572	MET	1HB	45.456	33.358	34.395	20.00
1573	MET	2HB	46.859	32.430	34.785	20.00
1574	MET	1HG	47.575	34.147	36.441	20.00
1575	MET	2HG	46.154	35.105	36.154	20.00
1576	MET	1HE	45.659	36.709	34.305	20.00
1577	MET	2HE	45.493	35.347	33.206	20.00
1578	MET	3HE	46.520	36.723	32.753	20.00
1579	VAL	N	43.503	33.877	37.018	12.17
1580	VAL	CA	42.734	34.719	37.923	10.63
1581	VAL	C	42.543	33.925	39.336	13.77
1582	VAL	O	42.754	34.422	40.455	14.26
1583	VAL	CB	41.481	35.257	37.215	10.58
1584	VAL	CG1	41.931	36.174	36.095	8.22
1585	VAL	CG2	40.524	36.097	38.147	10.48
1586	VAL	H	43.171	33.627	36.109	20.00
1587	VAL	HA	43.374	35.574	38.158	20.00
1588	VAL	HB	40.927	34.414	36.800	20.00
1589	VAL	1HG1	42.614	35.675	35.400	20.00
1590	VAL	2HG1	42.457	37.043	36.488	20.00
1591	VAL	3HG1	41.073	36.507	35.505	20.00
1592	VAL	1HG2	41.087	36.909	38.606	20.00
1593	VAL	2HG2	40.113	35.494	38.956	20.00
1594	VAL	3HG2	39.722	36.595	37.623	20.00
1595	TRP	N	42.224	32.627	39.175	13.52
1596	TRP	CA	42.001	31.790	40.338	14.59
1597	TRP	C	43.264	31.610	41.155	15.04
1598	TRP	O	43.328	32.070	42.288	16.22
1599	TRP	CB	41.340	30.544	39.858	12.97
1600	TRP	CG	40.867	29.820	41.069	17.46
1601	TRP	CD1	41.606	28.897	41.786	21.61
1602	TRP	CD2	39.602	29.940	41.731	19.79

1603	TRP	NE1	40.899	28.456	42.861	23.85
1604	TRP	CE2	39.653	29.065	42.870	22.70
1605	TRP	CE3	38.464	30.605	41.428	21.09
1606	TRP	CZ2	38.576	28.895	43.700	21.76
1607	TRP	CZ3	37.360	30.412	42.267	21.15
1608	TRP	CH2	37.413	29.570	43.399	21.23
1609	TRP	H	42.074	32.302	38.246	20.00
1610	TRP	HA	41.294	32.332	40.966	20.00
1611	TRP	1HB	42.030	29.916	39.289	20.00
1612	TRP	2HB	40.487	30.754	39.199	20.00
1613	TRP	HD1	42.618	28.612	41.516	20.00
1614	TRP	HE1	41.220	27.834	43.554	20.00
1615	TRP	HE3	38.407	31.218	40.555	20.00
1616	TRP	HZ2	38.667	28.250	44.569	20.00
1617	TRP	HZ3	36.437	30.916	42.045	20.00
1618	TRP	HH2	36.555	29.455	44.032	20.00
1619	GLU	N	44.259	30.940	40.543	16.06
1620	GLU	CA	45.592	30.695	41.135	15.05
1621	GLU	C	46.223	31.929	41.826	16.50
1622	GLU	O	46.831	31.834	42.894	18.37
1623	GLU	CB	46.473	30.020	40.099	13.43
1624	GLU	CG	45.967	28.568	39.973	13.77
1625	GLU	CD	46.558	27.837	38.747	14.43
1626	GLU	OE1	47.458	28.382	38.119	15.87
1627	GLU	OE2	46.113	26.745	38.435	15.61
1628	GLU	H	44.114	30.564	39.620	20.00
1629	GLU	HA	45.422	29.979	41.932	20.00
1630	GLU	1HB	47.522	30.030	40.407	20.00
1631	GLU	2HB	46.364	30.567	39.152	20.00
1632	GLU	1HG	44.895	28.546	39.840	20.00
1633	GLU	2HG	46.191	27.991	40.858	20.00
1634	GLN	N	45.999	33.062	41.202	14.99
1635	GLN	CA	46.714	34.258	41.610	14.10
1636	GLN	C	45.841	35.103	42.496	14.79
1637	GLN	O	46.292	36.113	42.957	14.03
1638	GLN	CB	47.074	35.107	40.341	13.84
1639	GLN	CG	48.001	34.423	39.298	14.77
1640	GLN	CD	49.291	33.960	40.073	20.12
1641	GLN	OE1	49.843	34.780	40.814	21.85
1642	GLN	NE2	49.740	32.664	39.964	18.11
1643	GLN	H	45.582	33.013	40.294	20.00
1644	GLN	HA	47.620	34.012	42.178	20.00
1645	GLN	1HB	47.560	36.034	40.653	20.00
1646	GLN	2HB	46.157	35.450	39.856	20.00
1647	GLN	1HG	48.269	35.110	38.493	20.00
1648	GLN	2HG	47.536	33.553	38.850	20.00
1649	GLN	1HE2	50.530	32.405	40.514	20.00
1650	GLN	2HE2	49.411	31.946	39.364	20.00
1651	LYS	N	44.583	34.682	42.756	14.24
1652	LYS	CA	43.720	35.355	43.752	15.01
1653	LYS	C	43.390	36.821	43.456	12.96
1654	LYS	O	43.245	37.665	44.331	13.31

1655	LYS	CB	44.218	35.116	45.226	19.21
1656	LYS	CG	44.427	33.587	45.521	21.85
1657	LYS	CD	44.580	33.241	47.008	29.47
1658	LYS	CE	45.043	31.802	47.295	31.82
1659	LYS	NZ	46.358	31.625	46.658	37.86
1660	LYS	H	44.246	33.917	42.208	20.00
1661	LYS	HA	42.775	34.834	43.635	20.00
1662	LYS	1HB	43.461	35.509	45.903	20.00
1663	LYS	2HB	45.135	35.675	45.430	20.00
1664	LYS	1HG	45.269	33.231	44.929	20.00
1665	LYS	2HG	43.538	33.081	45.155	20.00
1666	LYS	1HD	43.644	33.429	47.532	20.00
1667	LYS	2HD	45.293	33.928	47.452	20.00
1668	LYS	1HE	44.353	31.026	46.952	20.00
1669	LYS	2HE	45.156	31.662	48.378	20.00
1670	LYS	1HZ	47.041	32.309	47.036	20.00
1671	LYS	2HZ	46.295	31.809	45.636	20.00
1672	LYS	3HZ	46.730	30.665	46.798	20.00
1673	SER	N	43.292	37.085	42.172	14.72
1674	SER	CA	42.944	38.424	41.776	14.22
1675	SER	C	41.469	38.644	41.990	15.12
1676	SER	O	40.653	37.731	41.873	14.48
1677	SER	CB	43.222	38.649	40.258	12.78
1678	SER	OG	44.599	38.384	39.786	13.54
1679	SER	H	43.501	36.368	41.511	20.00
1680	SER	HA	43.424	39.132	42.463	20.00
1681	SER	1HB	42.684	39.566	39.862	20.00
1682	SER	2HB	42.553	37.916	39.760	20.00
1683	SER	HG	45.445	38.774	40.181	20.00
1684	ARG	N	41.194	39.943	42.269	13.87
1685	ARG	CA	39.838	40.374	42.565	14.62
1686	ARG	C	39.210	41.125	41.397	14.77
1687	ARG	O	38.037	41.061	41.111	13.72
1688	ARG	CB	39.935	41.251	43.846	14.39
1689	ARG	CG	38.548	41.299	44.523	23.02
1690	ARG	CD	37.577	42.376	44.071	27.49
1691	ARG	NE	36.501	42.588	45.040	30.20
1692	ARG	CZ	35.270	42.112	45.005	29.90
1693	ARG	NH1	34.915	40.949	44.459	31.36
1694	ARG	NH2	34.360	42.901	45.542	30.49
1695	ARG	H	41.983	40.543	42.411	20.00
1696	ARG	HA	39.228	39.487	42.741	20.00
1697	ARG	1HB	40.353	42.237	43.656	20.00
1698	ARG	2HB	40.624	40.744	44.518	20.00
1699	ARG	1HG	38.665	41.371	45.589	20.00
1700	ARG	2HG	38.050	40.344	44.361	20.00
1701	ARG	1HD	37.164	42.250	43.068	20.00
1702	ARG	2HD	38.127	43.313	44.077	20.00
1703	ARG	HE	36.646	43.361	45.657	20.00
1704	ARG	1HH1	33.929	40.756	44.381	20.00
1705	ARG	2HH1	35.573	40.273	44.127	20.00
1706	ARG	1HH2	33.407	42.577	45.455	20.00

1707	ARG	2HH2	34.560	43.766	45.978	20.00
1708	GLY	N	40.103	41.883	40.761	15.17
1709	GLY	CA	39.769	42.723	39.598	13.10
1710	GLY	C	40.451	42.232	38.273	12.93
1711	GLY	O	41.570	41.712	38.267	12.18
1712	GLY	H	41.036	41.839	41.124	20.00
1713	GLY	1HA	40.096	43.738	39.816	20.00
1714	GLY	2HA	38.686	42.743	39.482	20.00
1715	VAL	N	39.674	42.483	37.168	13.38
1716	VAL	CA	40.227	42.427	35.793	10.87
1717	VAL	C	39.995	43.725	35.172	9.66
1718	VAL	O	38.888	44.245	35.106	10.04
1719	VAL	CB	39.570	41.284	34.982	10.73
1720	VAL	CG1	39.639	39.894	35.612	11.72
1721	VAL	CG2	40.122	41.100	33.537	10.72
1722	VAL	H	38.722	42.761	37.332	20.00
1723	VAL	HA	41.295	42.251	35.853	20.00
1724	VAL	HB	38.516	41.544	34.929	20.00
1725	VAL	1HG1	39.229	39.859	36.619	20.00
1726	VAL	2HG1	40.675	39.558	35.682	20.00
1727	VAL	3HG1	39.100	39.172	34.999	20.00
1728	VAL	1HG2	41.197	40.918	33.522	20.00
1729	VAL	2HG2	39.948	41.984	32.925	20.00
1730	VAL	3HG2	39.637	40.265	33.032	20.00
1731	VAL	N	41.057	44.256	34.606	8.51
1732	VAL	CA	40.949	45.502	33.785	7.91
1733	VAL	C	41.098	45.261	32.275	8.39
1734	VAL	O	42.171	44.892	31.831	9.71
1735	VAL	CB	41.905	46.631	34.279	6.14
1736	VAL	CG1	41.684	47.022	35.734	7.70
1737	VAL	CG2	41.778	47.812	33.395	6.32
1738	VAL	H	41.884	43.822	34.895	20.00
1739	VAL	HA	39.938	45.889	33.912	20.00
1740	VAL	HB	42.928	46.278	34.202	20.00
1741	VAL	1HG1	41.809	46.162	36.389	20.00
1742	VAL	2HG1	40.681	47.425	35.882	20.00
1743	VAL	3HG1	42.394	47.791	36.054	20.00
1744	VAL	1HG2	40.751	48.182	33.347	20.00
1745	VAL	2HG2	42.150	47.616	32.391	20.00
1746	VAL	3HG2	42.380	48.634	33.780	20.00
1747	MET	N	40.029	45.551	31.499	8.82
1748	MET	CA	40.098	45.371	30.025	8.53
1749	MET	C	40.050	46.649	29.219	9.29
1750	MET	O	39.015	47.259	29.225	9.66
1751	MET	CB	38.784	44.680	29.671	8.63
1752	MET	CG	38.641	44.332	28.205	9.02
1753	MET	SD	37.443	43.055	27.893	13.59
1754	MET	CE	37.600	42.908	26.065	7.30
1755	MET	H	39.197	45.854	31.962	20.00
1756	MET	HA	40.941	44.743	29.751	20.00
1757	MET	1HB	37.913	45.199	30.067	20.00
1758	MET	2HB	38.900	43.841	30.315	20.00

1759	MET	1HG	39.586	43.983	27.797	20.00
1760	MET	2HG	38.320	45.209	27.645	20.00
1761	MET	1HE	38.649	42.746	25.840	20.00
1762	MET	2HE	37.313	43.833	25.576	20.00
1763	MET	3HE	37.023	42.066	25.702	20.00
1764	LEU	N	41.108	47.023	28.523	8.05
1765	LEU	CA	41.161	48.369	27.911	6.79
1766	LEU	C	40.878	48.480	26.338	8.29
1767	LEU	O	41.027	49.534	25.740	8.17
1768	LEU	CB	42.531	48.968	28.277	8.82
1769	LEU	CG	42.851	48.939	29.793	9.33
1770	LEU	CD1	41.825	49.803	30.601	6.68
1771	LEU	CD2	44.286	49.352	29.927	8.69
1772	LEU	H	41.914	46.450	28.660	20.00
1773	LEU	HA	40.405	48.977	28.396	20.00
1774	LEU	1HB	42.648	49.982	27.900	20.00
1775	LEU	2HB	43.278	48.364	27.763	20.00
1776	LEU	HG	42.807	47.915	30.157	20.00
1777	LEU	1HD1	40.826	49.357	30.594	20.00
1778	LEU	2HD1	41.756	50.793	30.148	20.00
1779	LEU	3HD1	42.127	49.940	31.640	20.00
1780	LEU	1HD2	44.381	50.415	29.708	20.00
1781	LEU	2HD2	44.933	48.881	29.208	20.00
1782	LEU	3HD2	44.686	49.148	30.922	20.00
1783	ASN	N	40.414	47.337	25.761	8.85
1784	ASN	CA	40.131	47.123	24.392	10.85
1785	ASN	C	38.659	46.635	24.231	10.96
1786	ASN	O	38.021	46.324	25.247	11.52
1787	ASN	CB	41.197	46.126	23.941	10.56
1788	ASN	CG	40.890	44.664	24.261	10.18
1789	ASN	OD1	40.432	43.836	23.484	13.30
1790	ASN	ND2	41.203	44.346	25.480	6.84
1791	ASN	H	39.979	46.747	26.435	20.00
1792	ASN	HA	40.182	48.082	23.880	20.00
1793	ASN	1HB	42.177	46.387	24.344	20.00
1794	ASN	2HB	41.276	46.154	22.858	20.00
1795	ASN	1HD2	41.057	43.367	25.597	20.00
1796	ASN	2HD2	41.445	44.908	26.261	20.00
1797	ARG	N	38.180	46.553	22.953	12.81
1798	ARG	CA	36.927	45.848	22.626	12.84
1799	ARG	C	37.350	44.502	22.051	13.06
1800	ARG	O	38.503	44.343	21.679	13.72
1801	ARG	CB	35.917	46.694	21.830	15.06
1802	ARG	CG	35.700	48.081	22.459	23.73
1803	ARG	CD	34.608	48.863	21.755	34.40
1804	ARG	NE	34.599	48.708	20.298	44.56
1805	ARG	CZ	35.344	49.461	19.525	51.42
1806	ARG	NH1	36.112	50.366	20.022	54.99
1807	ARG	NH2	35.346	49.337	18.230	53.99
1808	ARG	H	38.768	46.870	22.206	20.00
1809	ARG	HA	36.453	45.621	23.579	20.00
1810	ARG	1HB	34.965	46.180	21.772	20.00

1811	ARG	2HB	36.260	46.803	20.803	20.00
1812	ARG	1HG	36.626	48.660	22.436	20.00
1813	ARG	2HG	35.439	47.990	23.514	20.00
1814	ARG	1HD	34.562	49.917	22.003	20.00
1815	ARG	2HD	33.643	48.479	22.083	20.00
1816	ARG	HE	34.015	48.023	19.871	20.00
1817	ARG	1HH1	36.646	50.991	19.465	20.00
1818	ARG	2HH1	36.185	50.455	21.013	20.00
1819	ARG	1HH2	35.928	49.944	17.707	20.00
1820	ARG	2HH2	34.791	48.643	17.775	20.00
1821	VAL	N	36.412	43.522	22.089	13.43
1822	VAL	CA	36.678	42.221	21.443	16.12
1823	VAL	C	36.936	42.341	19.861	16.48
1824	VAL	O	37.508	41.501	19.204	14.56
1825	VAL	CB	35.416	41.364	21.767	14.79
1826	VAL	CG1	35.507	40.697	23.158	14.80
1827	VAL	CG2	35.222	40.300	20.662	16.58
1828	VAL	H	35.544	43.637	22.538	20.00
1829	VAL	HA	37.574	41.806	21.888	20.00
1830	VAL	HB	34.531	42.004	21.742	20.00
1831	VAL	1HG1	35.515	41.454	23.937	20.00
1832	VAL	2HG1	36.431	40.123	23.260	20.00
1833	VAL	3HG1	34.687	40.009	23.336	20.00
1834	VAL	1HG2	36.123	39.694	20.523	20.00
1835	VAL	2HG2	34.966	40.732	19.690	20.00
1836	VAL	3HG2	34.404	39.618	20.907	20.00
1837	MET	N	36.406	43.407	19.280	17.62
1838	MET	CA	36.626	43.711	17.914	19.41
1839	MET	C	36.901	45.186	17.748	17.22
1840	MET	O	36.164	46.011	18.235	16.41
1841	MET	CB	35.353	43.277	17.172	22.53
1842	MET	CG	35.669	43.239	15.645	30.44
1843	MET	SD	34.456	42.296	14.726	36.43
1844	MET	CE	33.433	43.769	14.332	32.23
1845	MET	H	35.921	44.042	19.872	20.00
1846	MET	HA	37.494	43.147	17.583	20.00
1847	MET	1HB	34.536	43.972	17.357	20.00
1848	MET	2HB	35.027	42.298	17.516	20.00
1849	MET	1HG	36.598	42.694	15.471	20.00
1850	MET	2HG	35.835	44.229	15.216	20.00
1851	MET	1HE	34.049	44.530	13.845	20.00
1852	MET	2HE	33.035	44.226	15.235	20.00
1853	MET	3HE	32.615	43.541	13.649	20.00
1854	GLU	N	37.970	45.511	17.065	17.49
1855	GLU	CA	38.300	46.936	16.903	18.64
1856	GLU	C	38.818	47.158	15.437	17.88
1857	GLU	O	39.395	46.229	14.856	18.32
1858	GLU	CB	39.271	47.483	17.997	16.54
1859	GLU	CG	39.163	46.802	19.374	16.82
1860	GLU	CD	40.244	47.335	20.294	15.94
1861	GLU	OE1	41.417	47.016	20.261	15.52
1862	GLU	OE2	39.878	48.107	21.133	15.98

1863	GLU	H	38.603	44.799	16.761	20.00
1864	GLU	HA	37.372	47.509	16.964	20.00
1865	GLU	1HB	39.171	48.563	18.106	20.00
1866	GLU	2HB	40.290	47.331	17.643	20.00
1867	GLU	1HG	39.267	45.731	19.339	20.00
1868	GLU	2HG	38.189	47.010	19.799	20.00
1869	LYS	N	38.446	48.382	14.874	19.17
1870	LYS	CA	38.777	48.777	13.484	20.14
1871	LYS	C	38.520	47.522	12.524	18.74
1872	LYS	O	39.311	47.173	11.670	18.86
1873	LYS	CB	40.278	49.240	13.415	21.50
1874	LYS	CG	40.703	50.654	13.986	24.11
1875	LYS	CD	42.172	50.552	14.578	28.82
1876	LYS	CE	43.021	51.809	14.894	30.30
1877	LYS	NZ	42.319	53.111	14.983	32.58
1878	LYS	H	37.978	49.029	15.463	20.00
1879	LYS	HA	38.115	49.580	13.155	20.00
1880	LYS	1HB	40.638	49.186	12.388	20.00
1881	LYS	2HB	40.863	48.468	13.917	20.00
1882	LYS	1HG	40.032	50.973	14.782	20.00
1883	LYS	2HG	40.674	51.390	13.184	20.00
1884	LYS	1HD	42.764	49.942	13.889	20.00
1885	LYS	2HD	42.152	49.930	15.476	20.00
1886	LYS	1HE	43.736	51.897	14.065	20.00
1887	LYS	2HE	43.661	51.644	15.777	20.00
1888	LYS	1HZ	41.751	53.142	15.851	20.00
1889	LYS	2HZ	41.700	53.243	14.157	20.00
1890	LYS	3HZ	43.009	53.887	15.036	20.00
1891	GLY	N	37.431	46.797	12.782	18.79
1892	GLY	CA	37.164	45.601	11.983	17.83
1893	GLY	C	37.939	44.317	12.298	19.02
1894	GLY	O	37.645	43.318	11.675	18.80
1895	GLY	H	36.805	47.142	13.472	20.00
1896	GLY	1HA	37.364	45.858	10.936	20.00
1897	GLY	2HA	36.104	45.378	12.101	20.00
1898	SER	N	38.905	44.320	13.292	16.08
1899	SER	CA	39.607	43.056	13.660	17.76
1900	SER	C	39.296	42.486	15.005	16.07
1901	SER	O	38.995	43.233	15.902	15.80
1902	SER	CB	41.114	43.073	13.410	21.32
1903	SER	OG	41.466	43.211	11.962	29.95
1904	SER	H	39.281	45.222	13.434	20.00
1905	SER	HA	39.189	42.275	13.020	20.00
1906	SER	1HB	41.468	42.062	13.716	20.00
1907	SER	2HB	41.685	43.644	14.204	20.00
1908	SER	HG	41.217	43.991	11.368	20.00
1909	LEU	N	39.354	41.139	15.085	16.19
1910	LEU	CA	39.179	40.408	16.344	14.22
1911	LEU	C	40.426	40.584	17.073	14.90
1912	LEU	O	41.500	40.325	16.507	16.30
1913	LEU	CB	38.953	38.890	16.239	13.16
1914	LEU	CG	37.613	38.637	15.495	12.66

1915	LEU	CD1	36.379	39.491	16.079	15.43
1916	LEU	CD2	37.330	37.112	15.281	13.88
1917	LEU	H	39.542	40.665	14.226	20.00
1918	LEU	HA	38.395	40.914	16.899	20.00
1919	LEU	1HB	38.892	38.447	17.234	20.00
1920	LEU	2HB	39.763	38.405	15.689	20.00
1921	LEU	HG	37.743	39.052	14.496	20.00
1922	LEU	1HD1	36.551	40.564	16.142	20.00
1923	LEU	2HD1	36.136	39.140	17.085	20.00
1924	LEU	3HD1	35.484	39.341	15.469	20.00
1925	LEU	1HD2	37.257	36.579	16.225	20.00
1926	LEU	2HD2	38.130	36.677	14.681	20.00
1927	LEU	3HD2	36.393	36.951	14.742	20.00
1928	LYS	N	40.213	41.120	18.298	14.30
1929	LYS	CA	41.214	41.721	19.186	11.19
1930	LYS	C	41.424	40.990	20.578	10.51
1931	LYS	O	42.491	41.101	21.208	11.24
1932	LYS	CB	40.927	43.219	19.400	11.90
1933	LYS	CG	41.294	44.096	18.204	15.22
1934	LYS	CD	42.782	44.088	18.074	16.86
1935	LYS	CE	43.416	44.879	16.995	20.26
1936	LYS	NZ	44.866	44.759	17.227	18.45
1937	LYS	H	39.250	41.290	18.494	20.00
1938	LYS	HA	42.072	41.565	18.549	20.00
1939	LYS	1HB	41.453	43.590	20.273	20.00
1940	LYS	2HB	39.873	43.359	19.638	20.00
1941	LYS	1HG	40.989	45.121	18.373	20.00
1942	LYS	2HG	40.822	43.779	17.280	20.00
1943	LYS	1HD	43.048	43.070	17.823	20.00
1944	LYS	2HD	43.172	44.442	19.028	20.00
1945	LYS	1HE	43.122	45.933	17.063	20.00
1946	LYS	2HE	43.135	44.495	16.012	20.00
1947	LYS	1HZ	45.192	43.803	17.446	20.00
1948	LYS	2HZ	45.137	45.336	18.077	20.00
1949	LYS	3HZ	45.463	45.200	16.489	20.00
1950	CYS	N	40.378	40.163	20.958	10.35
1951	CYS	CA	40.307	39.378	22.205	10.12
1952	CYS	C	39.140	38.345	22.075	13.34
1953	CYS	O	38.199	38.571	21.322	13.61
1954	CYS	CB	39.998	40.335	23.357	13.04
1955	CYS	SG	39.948	39.653	25.023	11.06
1956	CYS	H	39.554	40.270	20.385	20.00
1957	CYS	HA	41.260	38.903	22.390	20.00
1958	CYS	1HB	39.044	40.818	23.189	20.00
1959	CYS	2HB	40.715	41.148	23.356	20.00
1960	CYS	HG	41.059	39.958	25.695	20.00
1961	ALA	N	39.220	37.197	22.807	11.84
1962	ALA	CA	38.076	36.310	22.861	11.47
1963	ALA	C	36.942	36.970	23.673	13.20
1964	ALA	O	37.135	37.777	24.550	10.87
1965	ALA	CB	38.542	34.974	23.518	9.90
1966	ALA	H	39.961	37.072	23.467	20.00

1967	ALA	HA	37.727	36.169	21.837	20.00
1968	ALA	1HB	38.943	35.142	24.518	20.00
1969	ALA	2HB	39.334	34.524	22.920	20.00
1970	ALA	3HB	37.722	34.257	23.606	20.00
1971	GLN	N	35.725	36.522	23.415	12.25
1972	GLN	CA	34.645	36.830	24.422	13.18
1973	GLN	C	34.789	35.908	25.674	13.71
1974	GLN	O	34.306	34.800	25.733	14.92
1975	GLN	CB	33.424	36.554	23.562	13.64
1976	GLN	CG	32.149	37.021	24.112	14.19
1977	GLN	CD	32.229	38.437	24.551	14.78
1978	GLN	OE1	32.151	38.741	25.725	20.52
1979	GLN	NE2	32.162	39.286	23.542	13.59
1980	GLN	H	35.602	35.916	22.635	20.00
1981	GLN	HA	34.723	37.882	24.718	20.00
1982	GLN	1HB	33.359	35.487	23.379	20.00
1983	GLN	2HB	33.554	37.017	22.589	20.00
1984	GLN	1HG	31.839	36.429	24.969	20.00
1985	GLN	2HG	31.338	36.929	23.379	20.00
1986	GLN	1HE2	31.885	40.195	23.842	20.00
1987	GLN	2HE2	32.304	39.058	22.593	20.00
1988	TYR	N	35.597	36.366	26.628	12.19
1989	TYR	CA	36.060	35.379	27.613	11.14
1990	TYR	C	35.168	35.400	28.882	10.72
1991	TYR	O	35.292	34.588	29.784	12.61
1992	TYR	CB	37.551	35.557	27.877	10.70
1993	TYR	CG	37.814	36.894	28.483	12.19
1994	TYR	CD1	37.736	37.113	29.882	10.21
1995	TYR	CD2	38.194	37.946	27.679	11.16
1996	TYR	CE1	38.060	38.311	30.487	12.37
1997	TYR	CE2	38.525	39.175	28.244	10.83
1998	TYR	CZ	38.452	39.353	29.637	11.09
1999	TYR	OH	38.741	40.615	30.127	11.70
2000	TYR	H	36.006	37.267	26.500	20.00
2001	TYR	HA	35.959	34.369	27.208	20.00
2002	TYR	1HB	38.106	35.477	26.945	20.00
2003	TYR	2HB	37.949	34.775	28.517	20.00
2004	TYR	HD1	37.433	36.298	30.508	20.00
2005	TYR	HD2	38.288	37.831	26.601	20.00
2006	TYR	HE1	38.028	38.353	31.577	20.00
2007	TYR	HE2	38.875	39.932	27.553	20.00
2008	TYR	HH	37.890	41.054	30.183	20.00
2009	TRP	N	34.243	36.345	28.877	11.94
2010	TRP	CA	33.260	36.444	29.897	12.84
2011	TRP	C	31.795	36.329	29.296	14.59
2012	TRP	O	31.599	36.587	28.134	14.57
2013	TRP	CB	33.665	37.712	30.717	12.85
2014	TRP	CG	33.087	38.918	30.092	13.65
2015	TRP	CD1	31.828	39.488	30.403	14.58
2016	TRP	CD2	33.657	39.662	29.006	12.43
2017	TRP	NE1	31.613	40.540	29.550	14.02
2018	TRP	CE2	32.726	40.705	28.701	12.63

2019	TRP	CE3	34.809	39.538	28.302	13.32		
2020	TRP	CZ2	33.067	41.598	27.737	12.31		
2021	TRP	CZ3	35.137	40.434	27.306	11.49		
2022	TRP	CH2	34.278	41.483	27.035	14.96		
2023	TRP	H	34.167	36.958	28.097	20.00		
2024	TRP	HA	33.359	35.577	30.550	20.00		
2025	TRP	1HB	34.750	37.815	30.805	20.00		
2026	TRP	2HB	33.287	37.655	31.738	20.00		
2027	TRP	HD1	31.145	39.100	31.149	20.00		
2028	TRP	HE1	30.758	41.024	29.513	20.00		
2029	TRP	HE3	35.482	38.710	28.515	20.00		
2030	TRP	HZ2	32.368	42.385	27.492	20.00		
2031	TRP	HZ3	36.048	40.298	26.745	20.00		
2032	TRP	HH2	34.554	42.186	26.270	20.00		
2033	PRO	N	30.771	35.903	30.090	16.00		
2034	PRO	CA	29.379	35.863	29.628	15.76		
2035	PRO	C	28.711	37.188	29.393	16.40		
2036	PRO	O	28.872	38.116	30.195	18.51		
2037	PRO	CB	28.648	35.085	30.686	12.06		
2038	PRO	CG	29.535	35.324	31.918	15.79		
2039	PRO	CD	30.937	35.297	31.426	15.75		
2040	PRO	HA	29.331	35.310	28.691	20.00		
2041	PRO	1HB	28.646	34.019	30.437	20.00		
2042	PRO	2HB	27.601	35.373	30.852	20.00		
2043	PRO	1HG	29.349	36.293	32.360	20.00		
2044	PRO	2HG	29.365	34.566	32.684	20.00		
2045	PRO	1HD	31.323	34.282	31.325	20.00		
2046	PRO	2HD	31.591	35.885	32.067	20.00		
2047	GLN	N	27.952	37.249	28.248	18.99		
2048	GLN	CA	27.291	38.520	27.966	21.65		
2049	GLN	C	25.891	38.588	28.499	22.14		
2050	GLN	O	25.303	39.651	28.554	20.49		
2051	GLN	CB	27.240	38.783	26.497	26.00		
2052	GLN	CG	28.579	39.367	26.064	32.71		
2053	GLN	CD	28.474	39.304	24.551	36.57		
2054	GLN	OE1	28.270	38.247	23.966	35.28		
2055	GLN	NE2	28.566	40.493	23.988	40.87		
2056	GLN	H	28.103	36.536	27.563	20.00		
2057	GLN	HA	27.828	39.333	28.450	20.00		
2058	GLN	1HB	26.462	39.506	26.222	20.00		
2059	GLN	2HB	27.001	37.849	25.971	20.00		
2060	GLN	1HG	29.420	38.737	26.370	20.00		
2061	GLN	2HG	28.769	40.372	26.438	20.00		
2062	GLN	1HE2	28.441	40.574	23.007	20.00		
2063	GLN	2HE2	28.815	41.241	24.593	20.00		
2064	LYS	N	25.408	37.425	28.909	20.39		
2065	LYS	CA	24.255	37.495	29.783	19.10		
2066	LYS	C	24.218	36.437	30.788	16.46		
2067	LYS	O	24.860	35.417	30.584	16.58		
2068	LYS	CB	23.043	37.308	28.996	22.59		
2069	LYS	CG	22.991	36.049	28.192	24.94		
2070	LYS	CD	21.840	36.224	27.229	30.53		

2071	LYS	CE	21.248	37.656	27.135	32.07
2072	LYS	NZ	19.951	37.638	26.450	40.14
2073	LYS	H	25.913	36.568	28.818	20.00
2074	LYS	HA	24.207	38.466	30.286	20.00
2075	LYS	1HB	23.084	38.211	28.385	20.00
2076	LYS	2HB	22.156	37.389	29.639	20.00
2077	LYS	1HG	22.886	35.151	28.800	20.00
2078	LYS	2HG	23.896	35.943	27.603	20.00
2079	LYS	1HD	21.052	35.524	27.493	20.00
2080	LYS	2HD	22.158	35.907	26.237	20.00
2081	LYS	1HE	21.938	38.332	26.616	20.00
2082	LYS	2HE	21.014	38.102	28.111	20.00
2083	LYS	1HZ	19.364	37.019	27.058	20.00
2084	LYS	2HZ	20.056	37.233	25.501	20.00
2085	LYS	3HZ	19.574	38.608	26.433	20.00
2086	GLU	N	23.400	36.776	31.841	15.88
2087	GLU	CA	23.136	36.118	33.111	15.37
2088	GLU	C	22.807	34.620	32.974	15.69
2089	GLU	O	23.432	33.804	33.626	13.68
2090	GLU	CB	22.083	36.964	33.900	16.72
2091	GLU	CG	22.625	38.280	34.481	14.29
2092	GLU	CD	22.320	39.420	33.579	18.80
2093	GLU	OE1	22.205	39.180	32.359	21.62
2094	GLU	OE2	22.216	40.551	34.077	21.27
2095	GLU	H	22.923	37.629	31.683	20.00
2096	GLU	HA	24.072	36.180	33.655	20.00
2097	GLU	1HB	21.726	36.367	34.740	20.00
2098	GLU	2HB	21.182	37.117	33.295	20.00
2099	GLU	1HG	23.692	38.268	34.620	20.00
2100	GLU	2HG	22.172	38.502	35.438	20.00
2101	GLU	N	21.816	34.259	32.125	18.42
2102	GLU	CA	21.276	32.842	31.945	20.95
2103	GLU	C	22.156	31.928	31.090	20.76
2104	GLU	O	21.994	30.705	31.057	20.49
2105	GLU	CB	19.952	32.834	31.234	20.78
2106	GLU	CG	19.309	34.201	31.354	25.93
2107	GLU	CD	19.642	35.143	30.246	25.99
2108	GLU	OE1	19.653	34.697	29.122	28.63
2109	GLU	OE2	19.906	36.310	30.524	25.53
2110	GLU	H	21.335	35.045	31.723	20.00
2111	GLU	HA	21.174	32.451	32.958	20.00
2112	GLU	1HB	19.298	32.082	31.685	20.00
2113	GLU	2HB	20.022	32.547	30.179	20.00
2114	GLU	1HG	19.417	34.671	32.332	20.00
2115	GLU	2HG	18.245	34.072	31.265	20.00
2116	LYS	N	23.111	32.603	30.414	21.38
2117	LYS	CA	24.125	31.842	29.692	21.50
2118	LYS	C	25.526	31.935	30.345	21.97
2119	LYS	O	26.347	32.738	29.892	22.57
2120	LYS	CB	24.088	32.258	28.172	22.92
2121	LYS	CG	22.714	31.845	27.594	27.23
2122	LYS	CD	22.552	31.376	26.144	35.59

2123	LYS	CE	23.728	30.467	25.664	43.39
2124	LYS	NZ	24.007	29.243	26.485	46.48
2125	LYS	H	23.100	33.602	30.448	20.00
2126	LYS	HA	23.905	30.779	29.750	20.00
2127	LYS	1HB	24.907	31.743	27.668	20.00
2128	LYS	2HB	24.269	33.331	28.039	20.00
2129	LYS	1HG	21.975	32.616	27.813	20.00
2130	LYS	2HG	22.353	30.996	28.180	20.00
2131	LYS	1HD	22.496	32.263	25.506	20.00
2132	LYS	2HD	21.598	30.867	26.006	20.00
2133	LYS	1HE	24.630	31.088	25.626	20.00
2134	LYS	2HE	23.573	30.193	24.616	20.00
2135	LYS	1HZ	23.210	28.580	26.409	20.00
2136	LYS	2HZ	24.158	29.477	27.490	20.00
2137	LYS	3HZ	24.854	28.748	26.137	20.00
2138	GLU	N	25.773	31.078	31.373	21.26
2139	GLU	CA	27.139	30.999	31.912	22.94
2140	GLU	C	28.092	30.064	31.083	21.77
2141	GLU	O	27.645	29.223	30.310	23.33
2142	GLU	CB	27.231	30.453	33.369	22.83
2143	GLU	CG	26.205	29.525	33.954	28.82
2144	GLU	CD	25.370	28.477	33.224	29.12
2145	GLU	OE1	25.536	27.271	33.488	33.37
2146	GLU	OE2	24.429	28.906	32.545	28.44
2147	GLU	H	25.059	30.466	31.701	20.00
2148	GLU	HA	27.582	31.996	31.877	20.00
2149	GLU	1HB	27.261	31.330	34.014	20.00
2150	GLU	2HB	28.206	30.000	33.571	20.00
2151	GLU	1HG	25.454	30.212	34.324	20.00
2152	GLU	2HG	26.595	29.090	34.874	20.00
2153	MET	N	29.391	30.275	31.312	18.83
2154	MET	CA	30.416	29.603	30.511	17.54
2155	MET	C	31.128	28.585	31.349	19.07
2156	MET	O	31.491	28.947	32.433	20.58
2157	MET	CB	31.427	30.660	30.153	16.27
2158	MET	CG	30.870	31.714	29.186	16.56
2159	MET	SD	32.137	32.886	28.710	19.88
2160	MET	CE	33.223	31.855	27.860	18.70
2161	MET	H	29.589	30.862	32.098	20.00
2162	MET	HA	29.978	29.130	29.625	20.00
2163	MET	1HB	32.321	30.175	29.762	20.00
2164	MET	2HB	31.744	31.163	31.066	20.00
2165	MET	1HG	30.026	32.258	29.604	20.00
2166	MET	2HG	30.521	31.214	28.283	20.00
2167	MET	1HE	32.744	31.511	26.943	20.00
2168	MET	2HE	33.506	30.974	28.415	20.00
2169	MET	3HE	34.117	32.425	27.610	20.00
2170	ILE	N	31.339	27.348	30.934	18.63
2171	ILE	CA	32.211	26.451	31.678	20.60
2172	ILE	C	33.493	26.318	30.901	20.37
2173	ILE	O	33.409	26.217	29.700	23.05
2174	ILE	CB	31.480	25.129	31.975	24.01

2175	ILE	CG1	30.423	25.362	33.119	25.81
2176	ILE	CG2	32.435	24.026	32.386	24.90
2177	ILE	CD1	29.015	25.092	32.627	27.88
2178	ILE	H	30.974	27.074	30.050	20.00
2179	ILE	HA	32.485	26.885	32.636	20.00
2180	ILE	HB	30.985	24.804	31.061	20.00
2181	ILE	1HG1	30.463	26.402	33.452	20.00
2182	ILE	2HG1	30.652	24.754	34.001	20.00
2183	ILE	1HG2	33.016	24.304	33.266	20.00
2184	ILE	2HG2	33.118	23.779	31.571	20.00
2185	ILE	3HG2	31.883	23.113	32.621	20.00
2186	ILE	1HD1	28.917	24.029	32.403	20.00
2187	ILE	2HD1	28.793	25.634	31.710	20.00
2188	ILE	3HD1	28.264	25.343	33.374	20.00
2189	PHE	N	34.683	26.352	31.568	19.97
2190	PHE	CA	35.937	26.121	30.909	18.46
2191	PHE	C	36.319	24.745	31.318	19.73
2192	PHE	O	36.707	24.506	32.444	18.94
2193	PHE	CB	36.932	27.287	31.208	16.35
2194	PHE	CG	36.422	28.683	31.025	14.87
2195	PHE	CD1	36.522	29.299	29.779	13.55
2196	PHE	CD2	35.733	29.310	32.097	16.14
2197	PHE	CE1	35.830	30.461	29.569	14.72
2198	PHE	CE2	35.066	30.492	31.858	14.63
2199	PHE	CZ	35.099	31.052	30.579	14.92
2200	PHE	H	34.651	26.525	32.549	20.00
2201	PHE	HA	35.764	26.097	29.830	20.00
2202	PHE	1HB	37.703	27.282	30.445	20.00
2203	PHE	2HB	37.090	27.353	32.285	20.00
2204	PHE	HD1	37.082	28.849	28.984	20.00
2205	PHE	HD2	35.695	28.842	33.075	20.00
2206	PHE	HE1	35.848	30.933	28.597	20.00
2207	PHE	HE2	34.533	30.984	32.644	20.00
2208	PHE	HZ	34.566	31.975	30.381	20.00
2209	GLU	N	36.121	23.790	30.412	23.42
2210	GLU	CA	36.337	22.339	30.733	27.04
2211	GLU	C	37.729	21.979	30.888	26.67
2212	GLU	O	38.100	21.211	31.739	27.77
2213	GLU	CB	35.728	21.345	29.766	32.84
2214	GLU	CG	34.183	21.469	29.799	43.59
2215	GLU	CD	33.519	20.760	28.583	52.36
2216	GLU	OE1	33.847	21.115	27.436	54.69
2217	GLU	OE2	32.681	19.880	28.790	55.07
2218	GLU	H	35.751	24.069	29.529	20.00
2219	GLU	HA	35.881	22.173	31.709	20.00
2220	GLU	1HB	35.996	20.309	30.011	20.00
2221	GLU	2HB	36.098	21.541	28.755	20.00
2222	GLU	1HG	33.904	22.517	29.697	20.00
2223	GLU	2HG	33.744	21.100	30.727	20.00
2224	ASP	N	38.560	22.594	30.081	25.27
2225	ASP	CA	39.984	22.349	30.299	24.77
2226	ASP	C	40.545	22.756	31.677	24.82

2227	ASP	O	41.386	22.063	32.189	26.69
2228	ASP	CB	40.679	23.052	29.135	25.87
2229	ASP	CG	40.734	24.550	29.259	28.11
2230	ASP	OD1	39.805	25.153	29.754	27.95
2231	ASP	OD2	41.734	25.112	28.924	30.09
2232	ASP	H	38.274	23.318	29.453	20.00
2233	ASP	HA	40.119	21.276	30.225	20.00
2234	ASP	1HB	40.199	22.776	28.195	20.00
2235	ASP	2HB	41.699	22.679	29.067	20.00
2236	THR	N	40.124	23.834	32.305	22.69
2237	THR	CA	40.690	24.144	33.672	20.10
2238	THR	C	39.585	23.979	34.752	20.10
2239	THR	O	39.768	24.233	35.885	20.15
2240	THR	CB	41.135	25.633	33.587	18.17
2241	THR	OG1	40.007	26.430	33.110	15.16
2242	THR	CG2	42.544	25.763	32.851	16.50
2243	THR	H	39.685	24.464	31.679	20.00
2244	THR	HA	41.531	23.510	33.937	20.00
2245	THR	HB	41.412	25.917	34.651	20.00
2246	THR	HG1	39.736	26.169	32.225	20.00
2247	THR	1HG2	42.651	25.408	31.820	20.00
2248	THR	2HG2	43.224	25.098	33.381	20.00
2249	THR	3HG2	42.971	26.751	32.905	20.00
2250	ASN	N	38.400	23.517	34.414	21.38
2251	ASN	CA	37.484	23.164	35.497	23.28
2252	ASN	C	36.941	24.311	36.323	23.35
2253	ASN	O	36.879	24.212	37.538	24.28
2254	ASN	CB	38.125	22.180	36.450	27.97
2255	ASN	CG	37.063	21.199	36.881	32.19
2256	ASN	OD1	36.007	21.054	36.300	34.42
2257	ASN	ND2	37.398	20.416	37.882	31.14
2258	ASN	H	38.197	23.360	33.445	20.00
2259	ASN	HA	36.637	22.771	34.958	20.00
2260	ASN	1HB	38.630	22.649	37.291	20.00
2261	ASN	2HB	38.876	21.572	35.956	20.00
2262	ASN	1HD2	36.827	19.614	38.005	20.00
2263	ASN	2HD2	38.154	20.743	38.435	20.00
2264	LEU	N	36.523	25.343	35.557	22.74
2265	LEU	CA	36.054	26.662	36.015	21.67
2266	LEU	C	34.666	26.976	35.433	20.94
2267	LEU	O	34.360	26.609	34.348	21.39
2268	LEU	CB	37.062	27.693	35.512	21.84
2269	LEU	CG	38.192	28.179	36.501	23.27
2270	LEU	CD1	39.526	28.185	35.755	17.13
2271	LEU	CD2	38.304	27.532	37.894	21.62
2272	LEU	H	36.596	25.109	34.588	20.00
2273	LEU	HA	35.977	26.636	37.101	20.00
2274	LEU	1HB	36.570	28.580	35.111	20.00
2275	LEU	2HB	37.540	27.261	34.632	20.00
2276	LEU	HG	37.973	29.219	36.721	20.00
2277	LEU	1HD1	39.471	28.735	34.816	20.00
2278	LEU	2HD1	39.850	27.168	35.542	20.00

2279	LEU	3HD1	40.281	28.627	36.394	20.00
2280	LEU	1HD2	38.454	26.455	37.798	20.00
2281	LEU	2HD2	37.409	27.696	38.497	20.00
2282	LEU	3HD2	39.149	27.916	38.459	20.00
2283	LYS	N	33.788	27.630	36.164	21.10
2284	LYS	CA	32.465	28.108	35.683	19.53
2285	LYS	C	32.490	29.604	35.894	18.34
2286	LYS	O	33.087	30.091	36.832	20.22
2287	LYS	CB	31.333	27.455	36.480	20.94
2288	LYS	CG	29.922	27.807	36.039	22.87
2289	LYS	CD	28.975	26.839	36.717	29.27
2290	LYS	CE	27.555	27.322	37.117	32.16
2291	LYS	NZ	27.241	26.588	38.379	36.84
2292	LYS	H	34.067	27.812	37.110	20.00
2293	LYS	HA	32.356	27.890	34.626	20.00
2294	LYS	1HB	31.418	27.687	37.535	20.00
2295	LYS	2HB	31.452	26.379	36.378	20.00
2296	LYS	1HG	29.776	27.833	34.960	20.00
2297	LYS	2HG	29.738	28.789	36.395	20.00
2298	LYS	1HD	29.460	26.460	37.618	20.00
2299	LYS	2HD	28.872	25.967	36.075	20.00
2300	LYS	1HE	26.811	27.141	36.334	20.00
2301	LYS	2HE	27.560	28.394	37.332	20.00
2302	LYS	1HZ	28.022	26.733	39.071	20.00
2303	LYS	2HZ	27.136	25.563	38.252	20.00
2304	LYS	3HZ	26.383	26.914	38.881	20.00
2305	LEU	N	31.850	30.299	35.029	16.41
2306	LEU	CA	31.816	31.744	35.238	16.41
2307	LEU	C	30.414	32.310	34.879	16.89
2308	LEU	O	29.861	31.985	33.848	16.71
2309	LEU	CB	32.856	32.320	34.286	15.09
2310	LEU	CG	33.093	33.868	34.349	13.98
2311	LEU	CD1	33.803	34.225	33.001	15.42
2312	LEU	CD2	33.869	34.360	35.697	16.75
2313	LEU	H	31.410	29.830	34.259	20.00
2314	LEU	HA	32.044	32.013	36.257	20.00
2315	LEU	1HB	32.580	32.030	33.270	20.00
2316	LEU	2HB	33.813	31.832	34.474	20.00
2317	LEU	HG	32.130	34.370	34.324	20.00
2318	LEU	1HD1	33.298	33.816	32.134	20.00
2319	LEU	2HD1	34.821	33.849	32.995	20.00
2320	LEU	3HD1	33.860	35.305	32.873	20.00
2321	LEU	1HD2	34.834	33.868	35.776	20.00
2322	LEU	2HD2	33.302	34.161	36.605	20.00
2323	LEU	3HD2	34.065	35.433	35.659	20.00
2324	THR	N	29.882	33.181	35.720	17.65
2325	THR	CA	28.551	33.725	35.460	17.51
2326	THR	C	28.621	35.167	35.480	16.95
2327	THR	O	29.498	35.674	36.178	16.10
2328	THR	CB	27.606	33.300	36.590	15.94
2329	THR	OG1	27.778	31.872	36.920	15.73
2330	THR	CG2	26.172	33.301	36.033	17.67

2331	THR	H	30.415	33.344	36.554	20.00
2332	THR	HA	28.182	33.409	34.478	20.00
2333	THR	HB	27.496	34.079	37.426	20.00
2334	THR	HG1	28.648	31.469	37.142	20.00
2335	THR	1HG2	26.077	32.678	35.147	20.00
2336	THR	2HG2	25.823	34.300	35.797	20.00
2337	THR	3HG2	25.480	32.889	36.770	20.00
2338	LEU	N	27.703	35.781	34.691	15.85
2339	LEU	CA	27.556	37.232	34.739	16.51
2340	LEU	C	26.532	37.558	35.906	19.83
2341	LEU	O	25.356	37.257	35.814	20.59
2342	LEU	CB	27.158	37.822	33.324	15.58
2343	LEU	CG	26.882	39.324	33.346	15.08
2344	LEU	CD1	26.057	39.756	32.155	13.12
2345	LEU	CD2	28.113	40.188	33.679	15.75
2346	LEU	H	27.076	35.205	34.167	20.00
2347	LEU	HA	28.523	37.660	35.002	20.00
2348	LEU	1HB	26.279	37.289	32.972	20.00
2349	LEU	2HB	27.913	37.649	32.569	20.00
2350	LEU	HG	26.189	39.498	34.166	20.00
2351	LEU	1HD1	25.097	39.241	32.130	20.00
2352	LEU	2HD1	26.577	39.583	31.213	20.00
2353	LEU	3HD1	25.853	40.827	32.198	20.00
2354	LEU	1HD2	28.892	40.010	32.953	20.00
2355	LEU	2HD2	28.512	39.992	34.673	20.00
2356	LEU	3HD2	27.865	41.249	33.638	20.00
2357	ILE	N	27.041	38.159	37.021	18.46
2358	ILE	CA	26.043	38.466	38.063	18.30
2359	ILE	C	25.345	39.750	37.757	18.81
2360	ILE	O	24.145	39.889	37.903	19.41
2361	ILE	CB	26.654	38.493	39.445	17.44
2362	ILE	CG1	27.314	37.152	39.761	16.16
2363	ILE	CG2	25.700	38.914	40.537	17.37
2364	ILE	CD1	26.469	35.848	39.622	15.26
2365	ILE	H	28.018	38.357	37.091	20.00
2366	ILE	HA	25.263	37.704	38.059	20.00
2367	ILE	HB	27.457	39.233	39.436	20.00
2368	ILE	1HG1	27.712	37.198	40.771	20.00
2369	ILE	2HG1	28.194	37.048	39.123	20.00
2370	ILE	1HG2	24.902	38.179	40.612	20.00
2371	ILE	2HG2	25.274	39.901	40.363	20.00
2372	ILE	3HG2	26.190	38.945	41.509	20.00
2373	ILE	1HD1	26.117	35.706	38.599	20.00
2374	ILE	2HD1	25.604	35.841	40.288	20.00
2375	ILE	3HD1	27.069	34.972	39.875	20.00
2376	SER	N	26.099	40.697	37.346	18.02
2377	SER	CA	25.432	41.954	36.914	19.40
2378	SER	C	26.370	42.826	36.013	21.38
2379	SER	O	27.551	42.619	36.115	22.64
2380	SER	CB	25.076	42.740	38.219	21.28
2381	SER	OG	26.035	43.743	38.695	24.51
2382	SER	H	27.087	40.552	37.291	20.00

2383	SER	HA	24.533	41.708	36.356	20.00
2384	SER	1HB	24.803	42.025	39.038	20.00
2385	SER	2HB	24.053	43.172	38.066	20.00
2386	SER	HG	26.904	43.995	38.253	20.00
2387	GLU	N	25.933	43.809	35.222	22.91
2388	GLU	CA	26.837	44.927	34.671	25.57
2389	GLU	C	26.217	46.306	34.923	25.11
2390	GLU	O	25.011	46.358	34.981	28.12
2391	GLU	CB	27.228	44.878	33.158	27.94
2392	GLU	CG	26.075	44.442	32.355	32.29
2393	GLU	CD	26.377	44.181	30.922	38.30
2394	GLU	OE1	27.547	44.144	30.531	43.02
2395	GLU	OE2	25.405	43.982	30.205	41.87
2396	GLU	H	24.982	43.809	34.916	20.00
2397	GLU	HA	27.770	44.930	35.236	20.00
2398	GLU	1HB	27.987	44.106	33.047	20.00
2399	GLU	2HB	27.650	45.808	32.773	20.00
2400	GLU	1HG	25.222	45.118	32.423	20.00
2401	GLU	2HG	25.745	43.467	32.706	20.00
2402	ASP	N	27.039	47.342	35.079	20.31
2403	ASP	CA	26.705	48.761	35.113	18.75
2404	ASP	C	27.443	49.451	33.921	19.30
2405	ASP	O	28.624	49.821	33.900	17.85
2406	ASP	CB	27.189	49.177	36.507	21.92
2407	ASP	CG	27.254	50.675	36.768	28.13
2408	ASP	OD1	26.258	51.344	36.462	28.01
2409	ASP	OD2	28.321	51.154	37.274	33.77
2410	ASP	H	28.005	47.105	35.158	20.00
2411	ASP	HA	25.624	48.883	35.026	20.00
2412	ASP	1HB	28.199	48.802	36.674	20.00
2413	ASP	2HB	26.569	48.727	37.282	20.00
2414	ILE	N	26.646	49.500	32.878	19.47
2415	ILE	CA	27.011	50.169	31.640	20.98
2416	ILE	C	26.884	51.689	31.756	22.51
2417	ILE	O	25.854	52.187	32.173	25.15
2418	ILE	CB	26.054	49.679	30.540	22.51
2419	ILE	CG1	26.166	48.190	30.336	22.32
2420	ILE	CG2	26.210	50.376	29.202	23.73
2421	ILE	CD1	25.344	47.693	29.157	22.61
2422	ILE	H	25.726	49.152	33.013	20.00
2423	ILE	HA	28.044	49.924	31.444	20.00
2424	ILE	HB	25.034	49.883	30.893	20.00
2425	ILE	1HG1	25.831	47.659	31.231	20.00
2426	ILE	2HG1	27.204	47.891	30.185	20.00
2427	ILE	1HG2	26.990	49.941	28.588	20.00
2428	ILE	2HG2	26.412	51.439	29.278	20.00
2429	ILE	3HG2	25.287	50.309	28.630	20.00
2430	ILE	1HD1	25.810	47.995	28.217	20.00
2431	ILE	2HD1	24.316	48.054	29.173	20.00
2432	ILE	3HD1	25.309	46.600	29.147	20.00
2433	LYS	N	27.927	52.396	31.334	21.11
2434	LYS	CA	28.007	53.844	31.411	20.45

2435	LYS	C	28.454	54.260	29.997	20.80
2436	LYS	O	28.625	53.399	29.162	22.26
2437	LYS	CB	29.094	54.210	32.440	22.37
2438	LYS	CG	28.926	53.803	33.916	25.62
2439	LYS	CD	28.269	54.939	34.702	29.83
2440	LYS	CE	27.931	54.725	36.183	33.05
2441	LYS	NZ	27.390	56.048	36.625	35.32
2442	LYS	H	28.708	51.893	30.963	20.00
2443	LYS	HA	27.026	54.274	31.645	20.00
2444	LYS	1HB	29.330	55.273	32.393	20.00
2445	LYS	2HB	30.013	53.731	32.121	20.00
2446	LYS	1HG	29.915	53.631	34.341	20.00
2447	LYS	2HG	28.387	52.862	34.018	20.00
2448	LYS	1HD	27.317	55.140	34.208	20.00
2449	LYS	2HD	28.840	55.855	34.583	20.00
2450	LYS	1HE	28.821	54.455	36.758	20.00
2451	LYS	2HE	27.183	53.930	36.298	20.00
2452	LYS	1HZ	26.728	56.433	35.914	20.00
2453	LYS	2HZ	28.153	56.770	36.673	20.00
2454	LYS	3HZ	26.891	56.014	37.524	20.00
2455	THR	N	28.665	55.518	29.676	19.82
2456	THR	CA	28.839	55.815	28.253	21.59
2457	THR	C	30.207	55.342	27.586	20.83
2458	THR	O	30.252	54.972	26.399	22.59
2459	THR	CB	28.731	57.347	28.048	24.13
2460	THR	OG1	29.994	57.972	28.523	24.73
2461	THR	CG2	27.406	57.828	28.730	30.44
2462	THR	H	28.394	56.233	30.314	20.00
2463	THR	HA	28.017	55.332	27.719	20.00
2464	THR	HB	28.524	57.312	26.923	20.00
2465	THR	HG1	30.033	58.957	28.697	20.00
2466	THR	1HG2	27.363	57.757	29.806	20.00
2467	THR	2HG2	26.606	57.179	28.402	20.00
2468	THR	3HG2	27.015	58.808	28.421	20.00
2469	TYR	N	31.305	55.374	28.446	17.73
2470	TYR	CA	32.678	55.061	27.957	15.97
2471	TYR	C	33.341	53.758	28.591	15.46
2472	TYR	O	34.328	53.178	28.162	15.86
2473	TYR	CB	33.284	56.428	28.157	12.55
2474	TYR	CG	33.967	56.737	29.464	12.56
2475	TYR	CD1	33.364	57.603	30.382	14.70
2476	TYR	CD2	35.206	56.191	29.786	14.86
2477	TYR	CE1	33.908	57.950	31.591	15.48
2478	TYR	CE2	35.785	56.566	30.989	16.69
2479	TYR	CZ	35.129	57.413	31.908	16.96
2480	TYR	OH	35.664	57.737	33.129	15.71
2481	TYR	H	31.090	55.949	29.230	20.00
2482	TYR	HA	32.616	54.883	26.881	20.00
2483	TYR	1HB	32.511	57.176	28.055	20.00
2484	TYR	2HB	33.813	56.779	27.310	20.00
2485	TYR	HD1	32.439	58.052	30.168	20.00
2486	TYR	HD2	35.662	55.472	29.127	20.00

2487	TYR	HE1	33.342	58.642	32.206	20.00
2488	TYR	HE2	36.782	56.174	31.160	20.00
2489	TYR	HH	35.472	57.124	33.840	20.00
2490	TYR	N	32.720	53.248	29.650	14.74
2491	TYR	CA	33.167	52.050	30.352	14.03
2492	TYR	C	31.906	51.359	30.862	16.12
2493	TYR	O	30.824	51.930	30.915	17.82
2494	TYR	CB	34.251	52.412	31.375	12.74
2495	TYR	CG	33.728	53.134	32.579	15.40
2496	TYR	CD1	33.475	52.431	33.758	13.77
2497	TYR	CD2	33.476	54.490	32.544	18.58
2498	TYR	CE1	33.015	53.078	34.883	15.81
2499	TYR	CE2	32.944	55.161	33.649	17.84
2500	TYR	CZ	32.740	54.435	34.866	16.69
2501	TYR	OH	32.240	54.871	36.111	18.92
2502	TYR	H	31.850	53.689	29.886	20.00
2503	TYR	HA	33.628	51.368	29.650	20.00
2504	TYR	1HB	35.016	53.026	30.901	20.00
2505	TYR	2HB	34.748	51.510	31.713	20.00
2506	TYR	HD1	33.656	51.367	33.806	20.00
2507	TYR	HD2	33.632	55.018	31.619	20.00
2508	TYR	HE1	32.854	52.539	35.807	20.00
2509	TYR	HE2	32.615	56.155	33.358	20.00
2510	TYR	HH	31.864	55.766	36.179	20.00
2511	THR	N	32.096	50.092	31.166	14.21
2512	THR	CA	31.125	49.193	31.834	15.42
2513	THR	C	31.889	48.540	33.043	15.44
2514	THR	O	33.128	48.344	32.955	15.14
2515	THR	CB	30.572	48.077	30.896	16.15
2516	THR	OG1	29.894	48.442	29.632	16.75
2517	THR	CG2	29.525	47.168	31.562	15.21
2518	THR	H	33.038	49.794	31.028	20.00
2519	THR	HA	30.320	49.806	32.254	20.00
2520	THR	HB	31.408	47.328	30.806	20.00
2521	THR	HG1	30.097	49.274	29.118	20.00
2522	THR	1HG2	28.699	47.761	31.955	20.00
2523	THR	2HG2	29.934	46.590	32.391	20.00
2524	THR	3HG2	29.096	46.451	30.861	20.00
2525	VAL	N	31.079	48.256	34.137	14.25
2526	VAL	CA	31.584	47.499	35.318	15.61
2527	VAL	C	30.715	46.291	35.625	15.76
2528	VAL	O	29.577	46.421	36.050	16.87
2529	VAL	CB	31.794	48.216	36.666	15.56
2530	VAL	CG1	32.554	49.567	36.570	17.93
2531	VAL	CG2	32.587	47.191	37.535	15.84
2532	VAL	H	30.179	48.701	34.161	20.00
2533	VAL	HA	32.559	47.126	35.001	20.00
2534	VAL	HB	30.835	48.422	37.142	20.00
2535	VAL	1HG1	31.976	50.307	36.013	20.00
2536	VAL	2HG1	33.491	49.416	36.039	20.00
2537	VAL	3HG1	32.779	49.960	37.562	20.00
2538	VAL	1HG2	33.506	46.870	37.041	20.00

2539	VAL	2HG2	32.017	46.297	37.790	20.00
2540	VAL	3HG2	32.878	47.622	38.492	20.00
2541	ARG	N	31.313	45.111	35.451	15.23
2542	ARG	CA	30.636	43.909	35.796	12.90
2543	ARG	C	31.149	43.269	37.138	14.57
2544	ARG	O	32.271	43.418	37.622	14.51
2545	ARG	CB	30.918	42.912	34.683	12.22
2546	ARG	CG	30.854	43.522	33.366	14.22
2547	ARG	CD	30.693	42.427	32.294	17.43
2548	ARG	NE	30.223	43.114	31.092	19.70
2549	ARG	CZ	30.925	43.891	30.263	18.02
2550	ARG	NH1	32.183	44.065	30.512	20.75
2551	ARG	NH2	30.350	44.466	29.248	22.30
2552	ARG	H	32.298	45.147	35.294	20.00
2553	ARG	HA	29.568	44.091	35.867	20.00
2554	ARG	1HB	30.145	42.142	34.759	20.00
2555	ARG	2HB	31.835	42.363	34.817	20.00
2556	ARG	1HG	31.731	44.132	33.167	20.00
2557	ARG	2HG	29.999	44.186	33.307	20.00
2558	ARG	1HD	29.921	41.721	32.566	20.00
2559	ARG	2HD	31.619	41.882	32.095	20.00
2560	ARG	HE	29.220	43.100	30.923	20.00
2561	ARG	1HH1	32.774	44.675	29.993	20.00
2562	ARG	2HH1	32.503	43.503	31.261	20.00
2563	ARG	1HH2	30.802	45.007	28.545	20.00
2564	ARG	2HH2	29.341	44.378	29.241	20.00
2565	GLN	N	30.217	42.477	37.624	15.95
2566	GLN	CA	30.475	41.509	38.662	15.20
2567	GLN	C	30.211	40.123	38.070	14.98
2568	GLN	O	29.185	39.776	37.459	15.16
2569	GLN	CB	29.451	41.789	39.755	19.99
2570	GLN	CG	29.683	40.991	41.063	24.39
2571	GLN	CD	28.589	41.388	42.123	33.29
2572	GLN	OE1	27.850	42.381	41.972	36.18
2573	GLN	NE2	28.425	40.476	43.095	32.20
2574	GLN	H	29.312	42.543	37.204	20.00
2575	GLN	HA	31.495	41.611	39.033	20.00
2576	GLN	1HB	28.462	41.527	39.400	20.00
2577	GLN	2HB	29.459	42.847	40.009	20.00
2578	GLN	1HG	30.642	41.250	41.495	20.00
2579	GLN	2HG	29.662	39.915	40.893	20.00
2580	GLN	1HE2	27.641	40.580	43.693	20.00
2581	GLN	2HE2	29.140	39.806	43.302	20.00
2582	LEU	N	31.219	39.366	38.295	14.40
2583	LEU	CA	31.301	38.012	37.806	16.50
2584	LEU	C	31.384	37.122	39.071	17.55
2585	LEU	O	31.940	37.484	40.119	18.19
2586	LEU	CB	32.603	37.945	36.952	16.87
2587	LEU	CG	32.569	38.220	35.452	19.16
2588	LEU	CD1	33.846	38.919	35.104	18.62
2589	LEU	CD2	31.412	39.019	34.876	19.45
2590	LEU	H	31.971	39.750	38.837	20.00

2591	LEU	HA	30.417	37.737	37.232	20.00
2592	LEU	1HB	32.962	36.918	37.027	20.00
2593	LEU	2HB	33.381	38.510	37.469	20.00
2594	LEU	HG	32.559	37.262	34.932	20.00
2595	LEU	1HD1	34.685	38.249	35.290	20.00
2596	LEU	2HD1	33.982	39.781	35.756	20.00
2597	LEU	3HD1	33.894	39.241	34.066	20.00
2598	LEU	1HD2	31.346	40.006	35.343	20.00
2599	LEU	2HD2	30.471	38.515	35.066	20.00
2600	LEU	3HD2	31.492	39.169	33.798	20.00
2601	GLU	N	30.823	35.909	38.869	16.26
2602	GLU	CA	31.238	34.878	39.789	16.63
2603	GLU	C	32.084	33.768	39.058	15.84
2604	GLU	O	31.620	33.130	38.137	17.35
2605	GLU	CB	30.001	34.344	40.415	17.38
2606	GLU	CG	30.495	33.228	41.347	23.65
2607	GLU	CD	29.265	32.786	42.113	30.56
2608	GLU	OE1	28.878	33.608	42.914	31.25
2609	GLU	OE2	28.700	31.723	41.893	32.96
2610	GLU	H	30.319	35.716	38.030	20.00
2611	GLU	HA	31.850	35.274	40.600	20.00
2612	GLU	1HB	29.288	33.951	39.680	20.00
2613	GLU	2HB	29.485	35.129	40.974	20.00
2614	GLU	1HG	31.213	33.593	42.076	20.00
2615	GLU	2HG	30.933	32.393	40.798	20.00
2616	LEU	N	33.326	33.595	39.566	17.81
2617	LEU	CA	34.140	32.449	39.349	19.00
2618	LEU	C	33.940	31.282	40.390	21.54
2619	LEU	O	34.276	31.393	41.532	19.81
2620	LEU	CB	35.606	32.971	39.327	17.55
2621	LEU	CG	36.442	32.660	38.027	19.65
2622	LEU	CD1	36.241	31.301	37.304	20.83
2623	LEU	CD2	37.930	32.956	38.354	17.35
2624	LEU	H	33.557	34.257	40.273	20.00
2625	LEU	HA	33.888	32.074	38.357	20.00
2626	LEU	1HB	36.140	32.604	40.202	20.00
2627	LEU	2HB	35.640	34.051	39.468	20.00
2628	LEU	HG	36.150	33.394	37.288	20.00
2629	LEU	1HD1	35.238	31.140	36.918	20.00
2630	LEU	2HD1	36.429	30.499	38.028	20.00
2631	LEU	3HD1	36.940	31.166	36.483	20.00
2632	LEU	1HD2	38.241	32.718	39.355	20.00
2633	LEU	2HD2	38.125	34.026	38.251	20.00
2634	LEU	3HD2	38.604	32.454	37.658	20.00
2635	GLU	N	33.496	30.126	39.911	24.40
2636	GLU	CA	33.575	28.858	40.619	24.80
2637	GLU	C	34.665	27.956	40.054	25.64
2638	GLU	O	34.768	27.641	38.858	24.49
2639	GLU	CB	32.249	28.090	40.382	24.55
2640	GLU	CG	31.925	27.011	41.455	26.49
2641	GLU	CD	30.506	26.410	41.400	28.97
2642	GLU	OE1	29.575	26.949	40.725	33.55

2643	GLU	OE2	30.384	25.331	42.024	32.02
2644	GLU	H	33.173	30.112	38.963	20.00
2645	GLU	HA	33.711	29.057	41.677	20.00
2646	GLU	1HB	32.211	27.646	39.397	20.00
2647	GLU	2HB	31.442	28.819	40.405	20.00
2648	GLU	1HG	32.032	27.435	42.451	20.00
2649	GLU	2HG	32.627	26.180	41.374	20.00
2650	ASN	N	35.429	27.522	41.022	26.33
2651	ASN	CA	36.257	26.375	40.918	28.36
2652	ASN	C	35.484	25.105	41.356	29.60
2653	ASN	O	35.519	24.635	42.483	31.34
2654	ASN	CB	37.592	26.666	41.584	27.93
2655	ASN	CG	38.437	25.448	41.952	30.21
2656	ASN	OD1	38.104	24.312	41.659	28.62
2657	ASN	ND2	39.585	25.727	42.536	31.76
2658	ASN	H	35.202	27.900	41.924	20.00
2659	ASN	HA	36.506	26.230	39.865	20.00
2660	ASN	1HB	37.424	27.336	42.384	20.00
2661	ASN	2HB	38.200	27.247	40.895	20.00
2662	ASN	1HD2	40.189	24.947	42.678	20.00
2663	ASN	2HD2	39.765	26.675	42.775	20.00
2664	LEU	N	34.921	24.563	40.253	30.56
2665	LEU	CA	34.285	23.303	40.064	31.30
2666	LEU	C	35.081	22.185	40.712	35.28
2667	LEU	O	34.408	21.328	41.256	35.62
2668	LEU	CB	34.110	23.167	38.540	28.95
2669	LEU	CG	32.712	23.388	37.955	29.38
2670	LEU	CD1	32.843	23.432	36.457	27.85
2671	LEU	CD2	32.026	24.649	38.417	30.00
2672	LEU	H	35.069	25.106	39.427	20.00
2673	LEU	HA	33.325	23.325	40.583	20.00
2674	LEU	1HB	34.448	22.177	38.227	20.00
2675	LEU	2HB	34.784	23.849	38.045	20.00
2676	LEU	HG	32.087	22.541	38.236	20.00
2677	LEU	1HD1	33.274	22.495	36.092	20.00
2678	LEU	2HD1	33.477	24.257	36.130	20.00
2679	LEU	3HD1	31.871	23.548	35.979	20.00
2680	LEU	1HD2	32.635	25.524	38.200	20.00
2681	LEU	2HD2	31.877	24.617	39.498	20.00
2682	LEU	3HD2	31.046	24.777	37.961	20.00
2683	THR	N	36.468	22.190	40.736	37.71
2684	THR	CA	37.202	21.155	41.533	41.16
2685	THR	C	36.825	21.148	43.051	43.17
2686	THR	O	36.644	20.102	43.667	45.18
2687	THR	CB	38.736	21.197	41.432	44.16
2688	THR	OG1	39.177	21.273	40.028	45.45
2689	THR	CG2	39.401	20.134	42.369	44.74
2690	THR	H	36.994	22.868	40.211	20.00
2691	THR	HA	36.832	20.195	41.169	20.00
2692	THR	HB	38.994	22.162	41.936	20.00
2693	THR	HG1	39.493	20.516	39.481	20.00
2694	THR	1HG2	39.074	19.099	42.217	20.00

2695	THR	2HG2	39.155	20.320	43.413	20.00
2696	THR	3HG2	40.498	20.158	42.403	20.00
2697	THR	N	36.755	22.357	43.620	43.51
2698	THR	CA	36.569	22.492	45.080	40.76
2699	THR	C	35.225	23.028	45.501	41.34
2700	THR	O	34.949	23.173	46.685	43.02
2701	THR	CB	37.422	23.692	45.561	39.25
2702	THR	OG1	37.152	25.022	44.987	42.09
2703	THR	CG2	38.908	23.417	45.377	37.92
2704	THR	H	36.887	23.135	43.004	20.00
2705	THR	HA	36.765	21.561	45.612	20.00
2706	THR	HB	37.364	23.699	46.689	20.00
2707	THR	HG1	36.526	25.122	44.220	20.00
2708	THR	1HG2	39.205	23.284	44.335	20.00
2709	THR	2HG2	39.175	22.506	45.911	20.00
2710	THR	3HG2	39.483	24.240	45.802	20.00
2711	GLN	N	34.476	23.431	44.476	40.94
2712	GLN	CA	33.352	24.345	44.557	41.20
2713	GLN	C	33.545	25.695	45.299	38.70
2714	GLN	O	32.586	26.414	45.546	38.13
2715	GLN	CB	32.149	23.549	45.037	45.37
2716	GLN	CG	31.786	22.523	43.980	51.51
2717	GLN	CD	30.414	21.959	44.267	56.44
2718	GLN	OE1	30.270	21.226	45.234	58.04
2719	GLN	NE2	29.438	22.272	43.407	61.09
2720	GLN	H	34.741	23.135	43.558	20.00
2721	GLN	HA	33.160	24.656	43.530	20.00
2722	GLN	1HB	31.310	24.234	45.188	20.00
2723	GLN	2HB	32.358	23.063	45.989	20.00
2724	GLN	1HG	32.495	21.702	43.926	20.00
2725	GLN	2HG	31.753	22.994	42.994	20.00
2726	GLN	1HE2	28.585	21.754	43.419	20.00
2727	GLN	2HE2	29.601	22.971	42.703	20.00
2728	GLU	N	34.762	26.092	45.656	37.29
2729	GLU	CA	34.911	27.514	46.023	37.74
2730	GLU	C	34.377	28.454	44.928	35.73
2731	GLU	O	34.427	28.209	43.728	34.94
2732	GLU	CB	36.317	27.954	46.489	43.18
2733	GLU	CG	36.377	29.427	47.019	51.01
2734	GLU	CD	37.799	29.866	47.427	57.11
2735	GLU	OE1	38.637	29.023	47.594	59.70
2736	GLU	OE2	38.063	31.062	47.546	59.23
2737	GLU	H	35.487	25.418	45.773	20.00
2738	GLU	HA	34.261	27.618	46.889	20.00
2739	GLU	1HB	37.020	27.876	45.674	20.00
2740	GLU	2HB	36.685	27.267	47.255	20.00
2741	GLU	1HG	35.747	29.531	47.902	20.00
2742	GLU	2HG	36.060	30.154	46.279	20.00
2743	THR	N	33.861	29.566	45.444	33.44
2744	THR	CA	33.250	30.618	44.592	31.67
2745	THR	C	33.937	31.934	44.874	30.34
2746	THR	O	34.285	32.227	46.011	31.62

2747	THR	CB	31.701	30.674	44.951	29.52
2748	THR	OG1	31.012	29.973	43.882	31.41
2749	THR	CG2	31.094	31.901	45.741	27.83
2750	THR	H	34.048	29.665	46.415	20.00
2751	THR	HA	33.482	30.372	43.553	20.00
2752	THR	HB	31.695	30.004	45.845	20.00
2753	THR	HG1	30.437	30.433	43.203	20.00
2754	THR	1HG2	31.122	32.846	45.187	20.00
2755	THR	2HG2	31.678	32.101	46.635	20.00
2756	THR	3HG2	30.068	31.750	46.091	20.00
2757	ARG	N	34.107	32.738	43.860	27.40
2758	ARG	CA	34.538	34.090	44.139	22.96
2759	ARG	C	33.959	35.067	43.175	19.60
2760	ARG	O	33.722	34.760	42.031	18.08
2761	ARG	CB	36.078	34.229	44.003	24.02
2762	ARG	CG	36.854	33.227	44.797	27.06
2763	ARG	CD	38.285	33.547	44.508	30.34
2764	ARG	NE	39.183	32.683	45.219	31.08
2765	ARG	CZ	40.370	32.287	44.813	33.27
2766	ARG	NH1	41.054	32.842	43.773	28.01
2767	ARG	NH2	40.742	31.202	45.477	34.77
2768	ARG	H	33.782	32.444	42.964	20.00
2769	ARG	HA	34.184	34.369	45.135	20.00
2770	ARG	1HB	36.387	35.247	44.261	20.00
2771	ARG	2HB	36.342	34.082	42.952	20.00
2772	ARG	1HG	36.606	32.197	44.535	20.00
2773	ARG	2HG	36.637	33.357	45.857	20.00
2774	ARG	1HD	38.521	34.562	44.846	20.00
2775	ARG	2HD	38.485	33.476	43.435	20.00
2776	ARG	HE	38.854	32.134	45.993	20.00
2777	ARG	1HH1	41.905	32.439	43.426	20.00
2778	ARG	2HH1	40.666	33.647	43.339	20.00
2779	ARG	1HH2	41.602	30.761	45.232	20.00
2780	ARG	2HH2	40.159	30.814	46.201	20.00
2781	GLU	N	33.859	36.255	43.731	19.61
2782	GLU	CA	33.468	37.442	43.053	20.49
2783	GLU	C	34.699	38.231	42.582	18.35
2784	GLU	O	35.609	38.648	43.324	19.50
2785	GLU	CB	32.651	38.383	43.905	23.73
2786	GLU	CG	32.354	39.674	43.116	30.58
2787	GLU	CD	31.697	40.680	44.039	37.37
2788	GLU	OE1	32.349	41.643	44.394	42.91
2789	GLU	OE2	30.572	40.459	44.434	39.95
2790	GLU	H	34.048	36.277	44.708	20.00
2791	GLU	HA	32.845	37.134	42.209	20.00
2792	GLU	1HB	33.179	38.620	44.825	20.00
2793	GLU	2HB	31.718	37.904	44.224	20.00
2794	GLU	1HG	31.671	39.438	42.299	20.00
2795	GLU	2HG	33.211	40.145	42.652	20.00
2796	ILE	N	34.562	38.431	41.227	17.31
2797	ILE	CA	35.533	39.098	40.423	15.44
2798	ILE	C	34.806	40.329	39.820	13.03

2799	ILE	O	33.725	40.269	39.307	13.73
2800	ILE	CB	36.014	38.081	39.316	14.77
2801	ILE	CG1	36.469	36.717	39.808	13.99
2802	ILE	CG2	37.156	38.781	38.511	13.81
2803	ILE	CD1	37.777	36.731	40.616	13.39
2804	ILE	H	33.698	38.103	40.833	20.00
2805	ILE	HA	36.373	39.393	41.053	20.00
2806	ILE	HB	35.178	37.891	38.645	20.00
2807	ILE	1HG1	36.634	36.068	38.940	20.00
2808	ILE	2HG1	35.686	36.219	40.382	20.00
2809	ILE	1HG2	37.976	39.123	39.142	20.00
2810	ILE	2HG2	36.753	39.664	38.013	20.00
2811	ILE	3HG2	37.571	38.142	37.731	20.00
2812	ILE	1HD1	37.651	37.273	41.553	20.00
2813	ILE	2HD1	38.583	37.221	40.068	20.00
2814	ILE	3HD1	38.126	35.731	40.878	20.00
2815	LEU	N	35.437	41.444	39.855	9.92
2816	LEU	CA	34.934	42.684	39.281	10.85
2817	LEU	C	35.639	42.986	37.908	12.45
2818	LEU	O	36.823	42.846	37.768	13.72
2819	LEU	CB	35.395	43.657	40.382	11.52
2820	LEU	CG	34.233	43.955	41.312	17.76
2821	LEU	CD1	34.708	44.759	42.493	14.86
2822	LEU	CD2	33.503	42.721	41.757	15.60
2823	LEU	H	36.344	41.402	40.277	20.00
2824	LEU	HA	33.859	42.644	39.125	20.00
2825	LEU	1HB	35.739	44.594	39.965	20.00
2826	LEU	2HB	36.256	43.272	40.931	20.00
2827	LEU	HG	33.518	44.568	40.763	20.00
2828	LEU	1HD1	35.021	45.750	42.182	20.00
2829	LEU	2HD1	35.528	44.252	42.999	20.00
2830	LEU	3HD1	33.915	44.895	43.226	20.00
2831	LEU	1HD2	34.144	41.977	42.215	20.00
2832	LEU	2HD2	32.928	42.261	40.949	20.00
2833	LEU	3HD2	32.747	43.012	42.487	20.00
2834	HIS	N	34.933	43.394	36.894	10.68
2835	HIS	CA	35.545	43.475	35.600	11.55
2836	HIS	C	35.323	44.872	35.144	12.79
2837	HIS	O	34.194	45.266	34.919	14.70
2838	HIS	CB	34.788	42.489	34.668	11.04
2839	HIS	CG	35.263	42.384	33.227	9.68
2840	HIS	ND1	34.526	42.828	32.187	10.25
2841	HIS	CD2	36.429	41.786	32.744	10.64
2842	HIS	CE1	35.183	42.511	31.063	12.62
2843	HIS	NE2	36.329	41.906	31.409	11.21
2844	HIS	H	33.982	43.625	37.069	20.00
2845	HIS	HA	36.601	43.242	35.581	20.00
2846	HIS	1HB	33.743	42.742	34.647	20.00
2847	HIS	2HB	34.856	41.492	35.083	20.00
2848	HIS	HD1	33.677	43.272	32.321	20.00
2849	HIS	HD2	37.206	41.325	33.337	20.00
2850	HIS	HE1	34.876	42.676	30.032	20.00

2851	PHE	N	36.438	45.608	34.939	12.23
2852	PHE	CA	36.352	47.028	34.537	10.89
2853	PHE	C	36.685	47.113	33.028	13.34
2854	PHE	O	37.811	46.965	32.583	13.55
2855	PHE	CB	37.334	47.858	35.441	10.80
2856	PHE	CG	37.058	47.717	36.947	11.64
2857	PHE	CD1	37.655	46.741	37.702	11.60
2858	PHE	CD2	36.134	48.520	37.567	14.48
2859	PHE	CE1	37.264	46.493	39.006	12.91
2860	PHE	CE2	35.739	48.287	38.862	15.96
2861	PHE	CZ	36.291	47.267	39.581	13.40
2862	PHE	H	37.310	45.176	35.152	20.00
2863	PHE	HA	35.335	47.384	34.690	20.00
2864	PHE	1HB	37.275	48.922	35.204	20.00
2865	PHE	2HB	38.366	47.564	35.244	20.00
2866	PHE	HD1	38.413	46.112	37.256	20.00
2867	PHE	HD2	35.694	49.334	37.003	20.00
2868	PHE	HE1	37.715	45.660	39.525	20.00
2869	PHE	HE2	34.999	48.915	39.328	20.00
2870	PHE	HZ	35.930	47.074	40.572	20.00
2871	HIS	N	35.639	47.337	32.230	11.63
2872	HIS	CA	35.829	47.375	30.802	10.69
2873	HIS	C	35.809	48.820	30.319	11.28
2874	HIS	O	34.778	49.477	30.311	10.79
2875	HIS	CB	34.731	46.513	30.278	11.78
2876	HIS	CG	34.919	46.186	28.833	10.24
2877	HIS	ND1	35.782	46.799	27.957	13.45
2878	HIS	CD2	34.178	45.239	28.132	9.09
2879	HIS	CE1	35.554	46.232	26.766	8.49
2880	HIS	NE2	34.587	45.287	26.854	12.97
2881	HIS	H	34.770	47.509	32.693	20.00
2882	HIS	HA	36.801	46.952	30.534	20.00
2883	HIS	1HB	33.769	46.998	30.395	20.00
2884	HIS	2HB	34.712	45.579	30.833	20.00
2885	HIS	HD1	36.458	47.499	28.105	20.00
2886	HIS	HD2	33.424	44.566	28.470	20.00
2887	HIS	HE1	35.972	46.552	25.831	20.00
2888	TYR	N	36.961	49.274	29.879	10.13
2889	TYR	CA	37.059	50.545	29.109	11.53
2890	TYR	C	36.769	50.315	27.571	12.75
2891	TYR	O	37.466	49.547	26.883	11.94
2892	TYR	CB	38.465	51.130	29.407	12.91
2893	TYR	CG	38.500	52.618	29.205	14.41
2894	TYR	CD1	38.303	53.125	27.967	12.62
2895	TYR	CD2	38.816	53.503	30.229	14.67
2896	TYR	CE1	38.422	54.506	27.769	14.22
2897	TYR	CE2	38.884	54.882	30.077	15.77
2898	TYR	CZ	38.608	55.421	28.834	16.57
2899	TYR	OH	38.583	56.821	28.797	18.08
2900	TYR	H	37.739	48.639	29.964	20.00
2901	TYR	HA	36.319	51.229	29.522	20.00
2902	TYR	1HB	39.183	50.677	28.729	20.00

2903	TYR	2HB	38.782	50.884	30.426	20.00
2904	TYR	HD1	38.125	52.492	27.111	20.00
2905	TYR	HD2	39.029	53.064	31.176	20.00
2906	TYR	HE1	38.636	54.616	26.713	20.00
2907	TYR	HE2	39.100	55.550	30.901	20.00
2908	TYR	HH	38.117	57.229	28.064	20.00
2909	THR	N	35.664	50.941	27.075	13.66
2910	THR	CA	35.217	50.519	25.758	14.87
2911	THR	C	35.474	51.605	24.708	16.37
2912	THR	O	35.293	51.365	23.530	19.74
2913	THR	CB	33.766	50.067	25.763	13.92
2914	THR	OG1	32.985	51.270	25.886	14.21
2915	THR	CG2	33.452	48.853	26.638	14.13
2916	THR	H	35.138	51.598	27.614	20.00
2917	THR	HA	35.810	49.689	25.389	20.00
2918	THR	HB	33.665	49.671	24.715	20.00
2919	THR	HG1	32.608	51.609	26.739	20.00
2920	THR	1HG2	33.804	48.858	27.675	20.00
2921	THR	2HG2	33.975	48.036	26.159	20.00
2922	THR	3HG2	32.412	48.517	26.599	20.00
2923	THR	N	35.980	52.791	25.104	17.79
2924	THR	CA	36.277	53.829	24.097	17.71
2925	THR	C	37.780	54.268	23.978	17.22
2926	THR	O	38.171	55.337	23.501	19.49
2927	THR	CB	35.414	55.056	24.407	20.00
2928	THR	OG1	35.794	55.465	25.757	22.57
2929	THR	CG2	33.969	54.696	24.541	17.86
2930	THR	H	35.848	53.085	26.052	20.00
2931	THR	HA	35.998	53.464	23.110	20.00
2932	THR	HB	35.386	55.656	23.415	20.00
2933	THR	HG1	36.368	56.268	25.953	20.00
2934	THR	1HG2	33.838	53.994	25.327	20.00
2935	THR	2HG2	33.561	54.280	23.626	20.00
2936	THR	3HG2	33.378	55.567	24.814	20.00
2937	TRP	N	38.641	53.346	24.336	13.24
2938	TRP	CA	40.120	53.598	24.218	11.42
2939	TRP	C	40.640	52.873	22.987	11.23
2940	TRP	O	40.679	51.639	22.980	13.88
2941	TRP	CB	40.854	53.065	25.467	10.59
2942	TRP	CG	42.300	53.478	25.605	10.86
2943	TRP	CD1	43.194	53.926	24.620	10.44
2944	TRP	CD2	43.010	53.434	26.877	11.23
2945	TRP	NE1	44.399	54.166	25.165	11.38
2946	TRP	CE2	44.332	53.890	26.576	11.59
2947	TRP	CE3	42.647	53.113	28.170	12.73
2948	TRP	CZ2	45.251	54.034	27.615	9.06
2949	TRP	CZ3	43.596	53.268	29.207	11.86
2950	TRP	CH2	44.901	53.730	28.923	9.08
2951	TRP	H	38.223	52.591	24.823	20.00
2952	TRP	HA	40.290	54.667	24.218	20.00
2953	TRP	1HB	40.803	51.977	25.516	20.00
2954	TRP	2HB	40.369	53.437	26.358	20.00

2955	TRP	HD1	42.974	54.062	23.567	20.00
2956	TRP	HE1	45.198	54.476	24.680	20.00
2957	TRP	HE3	41.644	52.763	28.381	20.00
2958	TRP	HZ2	46.233	54.366	27.330	20.00
2959	TRP	HZ3	43.327	53.028	30.234	20.00
2960	TRP	HH2	45.624	53.867	29.709	20.00
2961	PRO	N	41.054	53.592	21.917	11.63
2962	PRO	CA	41.341	52.864	20.657	12.03
2963	PRO	C	42.762	52.223	20.620	10.91
2964	PRO	O	43.674	52.589	21.352	11.74
2965	PRO	CB	41.002	53.928	19.599	15.45
2966	PRO	CG	40.318	55.060	20.382	16.92
2967	PRO	CD	40.930	55.068	21.726	12.40
2968	PRO	HA	40.641	52.036	20.543	20.00
2969	PRO	1HB	40.376	53.540	18.790	20.00
2970	PRO	2HB	41.911	54.325	19.146	20.00
2971	PRO	1HG	40.429	56.033	19.909	20.00
2972	PRO	2HG	39.258	54.863	20.489	20.00
2973	PRO	1HD	40.296	55.584	22.434	20.00
2974	PRO	2HD	41.916	55.543	21.732	20.00
2975	ASP	N	42.866	51.223	19.711	9.83
2976	ASP	CA	44.171	50.530	19.648	13.50
2977	ASP	C	45.160	51.471	19.077	15.42
2978	ASP	O	44.802	52.201	18.172	16.15
2979	ASP	CB	44.065	49.223	18.819	14.19
2980	ASP	CG	45.153	48.241	19.221	17.10
2981	ASP	OD1	45.877	48.540	20.150	16.38
2982	ASP	OD2	45.270	47.155	18.676	16.84
2983	ASP	H	42.077	50.813	19.277	20.00
2984	ASP	HA	44.449	50.328	20.691	20.00
2985	ASP	1HB	44.135	49.419	17.751	20.00
2986	ASP	2HB	43.120	48.725	19.033	20.00
2987	PHE	N	46.329	51.527	19.651	15.66
2988	PHE	CA	47.349	52.538	19.450	13.22
2989	PHE	C	46.921	54.020	19.555	13.65
2990	PHE	O	47.504	54.923	18.956	14.13
2991	PHE	CB	48.233	52.272	18.290	15.03
2992	PHE	CG	48.749	50.895	18.233	16.37
2993	PHE	CD1	49.950	50.591	18.833	12.85
2994	PHE	CD2	48.009	49.927	17.529	15.04
2995	PHE	CE1	50.376	49.294	18.803	10.54
2996	PHE	CE2	48.460	48.659	17.407	12.82
2997	PHE	CZ	49.626	48.341	18.105	12.68
2998	PHE	H	46.546	50.666	20.113	20.00
2999	PHE	HA	47.975	52.405	20.321	20.00
3000	PHE	1HB	49.022	53.011	18.302	20.00
3001	PHE	2HB	47.662	52.452	17.380	20.00
3002	PHE	HD1	50.490	51.363	19.335	20.00
3003	PHE	HD2	47.070	50.181	17.066	20.00
3004	PHE	HE1	51.281	48.969	19.299	20.00
3005	PHE	HE2	47.901	47.906	16.873	20.00
3006	PHE	HZ	49.963	47.312	18.117	20.00

3007	GLY	N	45.887	54.153	20.424	12.17
3008	GLY	CA	45.240	55.436	20.680	12.74
3009	GLY	C	45.436	55.859	22.144	13.53
3010	GLY	O	46.132	55.250	22.953	12.80
3011	GLY	H	45.489	53.315	20.797	20.00
3012	GLY	1HA	44.176	55.267	20.536	20.00
3013	GLY	2HA	45.596	56.211	19.988	20.00
3014	VAL	N	44.801	56.938	22.435	14.29
3015	VAL	CA	44.812	57.503	23.722	13.36
3016	VAL	C	43.249	57.513	24.071	15.85
3017	VAL	O	42.426	57.380	23.136	16.84
3018	VAL	CB	45.673	58.788	23.744	12.64
3019	VAL	CG1	45.201	59.840	22.763	13.96
3020	VAL	CG2	47.178	58.444	23.585	12.56
3021	VAL	H	44.211	57.343	21.732	20.00
3022	VAL	HA	45.291	56.801	24.402	20.00
3023	VAL	HB	45.561	59.232	24.737	20.00
3024	VAL	1HG1	44.171	60.133	22.945	20.00
3025	VAL	2HG1	45.278	59.537	21.722	20.00
3026	VAL	3HG1	45.807	60.743	22.867	20.00
3027	VAL	1HG2	47.395	58.056	22.589	20.00
3028	VAL	2HG2	47.478	57.697	24.315	20.00
3029	VAL	3HG2	47.782	59.337	23.714	20.00
3030	PRO	N	42.963	57.517	25.476	16.09
3031	PRO	CA	41.668	57.936	26.088	14.29
3032	PRO	C	41.138	59.345	25.657	16.70
3033	PRO	O	41.887	60.270	25.348	15.47
3034	PRO	CB	42.035	58.106	27.586	12.24
3035	PRO	CG	43.260	57.208	27.767	11.83
3036	PRO	CD	44.019	57.339	26.463	14.99
3037	PRO	HA	40.885	57.194	25.936	20.00
3038	PRO	1HB	41.236	57.797	28.246	20.00
3039	PRO	2HB	42.288	59.134	27.841	20.00
3040	PRO	1HG	43.844	57.437	28.646	20.00
3041	PRO	2HG	42.915	56.182	27.868	20.00
3042	PRO	1HD	44.640	56.472	26.300	20.00
3043	PRO	2HD	44.642	58.226	26.489	20.00
3044	GLU	N	39.830	59.499	25.747	18.37
3045	GLU	CA	39.149	60.735	25.401	20.99
3046	GLU	C	39.701	61.877	26.121	22.01
3047	GLU	O	39.946	62.949	25.567	24.26
3048	GLU	CB	37.652	60.699	25.572	22.54
3049	GLU	CG	37.095	59.481	24.814	31.50
3050	GLU	CD	36.818	58.252	25.737	36.66
3051	GLU	OE1	37.792	57.706	26.363	31.28
3052	GLU	OE2	35.603	57.899	25.789	36.17
3053	GLU	H	39.307	58.672	25.934	20.00
3054	GLU	HA	39.384	60.894	24.354	20.00
3055	GLU	1HB	37.225	61.596	25.130	20.00
3056	GLU	2HB	37.322	60.660	26.604	20.00
3057	GLU	1HG	37.751	59.146	24.012	20.00
3058	GLU	2HG	36.147	59.734	24.345	20.00

3059	SER	N	39.960	61.603	27.399	20.38
3060	SER	CA	40.647	62.714	28.080	17.88
3061	SER	C	41.167	62.167	29.306	15.08
3062	SER	O	40.789	61.054	29.671	14.67
3063	SER	CB	39.666	63.853	28.431	16.14
3064	SER	OG	38.604	63.400	29.339	13.25
3065	SER	H	39.673	60.707	27.729	20.00
3066	SER	HA	41.461	63.055	27.454	20.00
3067	SER	1HB	39.386	64.462	27.511	20.00
3068	SER	2HB	40.217	64.669	28.926	20.00
3069	SER	HG	38.043	62.566	29.237	20.00
3070	PRO	N	42.046	62.978	29.961	17.02
3071	PRO	CA	42.562	62.555	31.277	16.44
3072	PRO	C	41.527	62.381	32.332	16.53
3073	PRO	O	41.596	61.476	33.162	15.74
3074	PRO	CB	43.653	63.578	31.636	16.53
3075	PRO	CG	43.993	64.277	30.294	18.72
3076	PRO	CD	42.716	64.193	29.431	16.72
3077	PRO	HA	43.044	61.584	31.179	20.00
3078	PRO	1HB	44.530	63.132	32.109	20.00
3079	PRO	2HB	43.256	64.327	32.324	20.00
3080	PRO	1HG	44.374	65.291	30.432	20.00
3081	PRO	2HG	44.794	63.718	29.803	20.00
3082	PRO	1HD	42.963	64.147	28.370	20.00
3083	PRO	2HD	42.115	65.075	29.631	20.00
3084	ALA	N	40.466	63.193	32.219	16.66
3085	ALA	CA	39.366	63.113	33.208	16.12
3086	ALA	C	38.576	61.824	33.103	15.23
3087	ALA	O	38.319	61.127	34.062	15.53
3088	ALA	CB	38.449	64.319	32.990	15.29
3089	ALA	H	40.478	63.899	31.513	20.00
3090	ALA	HA	39.809	63.153	34.207	20.00
3091	ALA	1HB	38.110	64.430	31.968	20.00
3092	ALA	2HB	38.976	65.236	33.241	20.00
3093	ALA	3HB	37.586	64.273	33.637	20.00
3094	SER	N	38.207	61.442	31.920	15.32
3095	SER	CA	37.563	60.086	31.870	15.79
3096	SER	C	38.482	58.892	32.167	13.45
3097	SER	O	38.104	57.921	32.825	13.08
3098	SER	CB	37.106	59.914	30.447	17.95
3099	SER	OG	38.030	60.657	29.618	26.88
3100	SER	H	38.374	62.009	31.111	20.00
3101	SER	HA	36.720	60.060	32.554	20.00
3102	SER	1HB	36.110	60.396	30.400	20.00
3103	SER	2HB	36.640	58.920	30.206	20.00
3104	SER	HG	38.996	60.405	29.428	20.00
3105	PHE	N	39.774	59.018	31.727	13.85
3106	PHE	CA	40.788	57.998	32.090	12.76
3107	PHE	C	40.881	57.892	33.605	12.10
3108	PHE	O	40.898	56.801	34.114	14.79
3109	PHE	CB	42.188	58.305	31.403	14.01
3110	PHE	CG	43.256	57.467	32.071	12.89

3111	PHE	CD1	43.459	56.157	31.644	10.70
3112	PHE	CD2	44.026	57.962	33.147	15.33
3113	PHE	CE1	44.455	55.390	32.240	13.65
3114	PHE	CE2	44.962	57.161	33.827	13.88
3115	PHE	CZ	45.203	55.884	33.321	14.38
3116	PHE	H	40.011	59.805	31.151	20.00
3117	PHE	HA	40.420	57.039	31.724	20.00
3118	PHE	1HB	42.428	59.353	31.538	20.00
3119	PHE	2HB	42.148	58.111	30.338	20.00
3120	PHE	HD1	42.865	55.751	30.834	20.00
3121	PHE	HD2	43.878	58.976	33.489	20.00
3122	PHE	HE1	44.653	54.393	31.863	20.00
3123	PHE	HE2	45.523	57.524	34.685	20.00
3124	PHE	HZ	45.964	55.260	33.765	20.00
3125	LEU	N	40.947	59.079	34.274	13.17
3126	LEU	CA	41.247	59.248	35.713	11.98
3127	LEU	C	40.029	58.870	36.513	11.69
3128	LEU	O	40.128	58.021	37.389	10.86
3129	LEU	CB	41.632	60.677	36.115	11.49
3130	LEU	CG	43.049	61.075	35.775	9.71
3131	LEU	CD1	44.161	60.504	36.812	12.65
3132	LEU	CD2	43.046	62.608	35.515	12.34
3133	LEU	H	40.884	59.875	33.675	20.00
3134	LEU	HA	42.051	58.546	35.951	20.00
3135	LEU	1HB	41.509	60.842	37.187	20.00
3136	LEU	2HB	40.927	61.358	35.635	20.00
3137	LEU	HG	43.285	60.627	34.817	20.00
3138	LEU	1HD1	44.121	59.416	36.874	20.00
3139	LEU	2HD1	43.969	60.871	37.820	20.00
3140	LEU	3HD1	45.175	60.780	36.532	20.00
3141	LEU	1HD2	42.831	63.130	36.448	20.00
3142	LEU	2HD2	42.314	62.959	34.794	20.00
3143	LEU	3HD2	44.031	62.930	35.184	20.00
3144	ASN	N	38.872	59.446	36.129	13.52
3145	ASN	CA	37.574	58.890	36.526	14.70
3146	ASN	C	37.456	57.332	36.437	13.68
3147	ASN	O	37.238	56.742	37.481	13.48
3148	ASN	CB	36.423	59.673	35.859	15.31
3149	ASN	CG	35.033	59.150	36.303	16.04
3150	ASN	OD1	34.813	59.091	37.511	17.67
3151	ASN	ND2	34.127	58.751	35.405	15.77
3152	ASN	H	38.965	60.202	35.486	20.00
3153	ASN	HA	37.544	59.107	37.591	20.00
3154	ASN	1HB	36.509	59.883	34.794	20.00
3155	ASN	2HB	36.434	60.658	36.318	20.00
3156	ASN	1HD2	33.321	58.374	35.886	20.00
3157	ASN	2HD2	34.246	58.811	34.418	20.00
3158	PHE	N	37.671	56.657	35.281	12.27
3159	PHE	CA	37.848	55.157	35.199	11.60
3160	PHE	C	38.826	54.528	36.216	11.61
3161	PHE	O	38.507	53.684	37.018	13.15
3162	PHE	CB	38.317	54.735	33.790	11.94

3163	PHE	CG	38.417	53.234	33.582	11.78
3164	PHE	CD1	39.644	52.558	33.626	14.00
3165	PHE	CD2	37.292	52.475	33.355	11.64
3166	PHE	CE1	39.718	51.158	33.535	10.61
3167	PHE	CE2	37.370	51.102	33.252	12.07
3168	PHE	CZ	38.565	50.426	33.352	10.24
3169	PHE	H	37.841	57.232	34.482	20.00
3170	PHE	HA	36.884	54.701	35.429	20.00
3171	PHE	1HB	39.285	55.186	33.567	20.00
3172	PHE	2HB	37.678	55.105	32.995	20.00
3173	PHE	HD1	40.553	53.144	33.746	20.00
3174	PHE	HD2	36.350	52.985	33.259	20.00
3175	PHE	HE1	40.676	50.645	33.599	20.00
3176	PHE	HE2	36.457	50.539	33.082	20.00
3177	PHE	HZ	38.602	49.351	33.281	20.00
3178	LEU	N	40.060	54.928	36.155	10.72
3179	LEU	CA	41.129	54.468	37.080	10.36
3180	LEU	C	40.671	54.520	38.579	11.41
3181	LEU	O	40.734	53.555	39.309	8.72
3182	LEU	CB	42.457	55.335	36.829	9.30
3183	LEU	CG	43.531	55.094	37.943	11.24
3184	LEU	CD1	44.819	55.890	37.855	9.97
3185	LEU	CD2	43.880	53.666	38.148	8.08
3186	LEU	H	40.230	55.612	35.446	20.00
3187	LEU	HA	41.306	53.427	36.811	20.00
3188	LEU	1HB	42.214	56.395	36.816	20.00
3189	LEU	2HB	42.881	55.113	35.846	20.00
3190	LEU	HG	43.084	55.415	38.883	20.00
3191	LEU	1HD1	44.605	56.957	37.902	20.00
3192	LEU	2HD1	45.361	55.713	36.926	20.00
3193	LEU	3HD1	45.489	55.647	38.679	20.00
3194	LEU	1HD2	44.339	53.255	37.248	20.00
3195	LEU	2HD2	43.033	53.027	38.390	20.00
3196	LEU	3HD2	44.625	53.549	38.936	20.00
3197	PHE	N	40.227	55.702	38.999	13.37
3198	PHE	CA	39.608	55.966	40.304	14.13
3199	PHE	C	38.419	55.074	40.584	14.10
3200	PHE	O	38.421	54.432	41.582	16.46
3201	PHE	CB	39.373	57.460	40.466	14.59
3202	PHE	CG	40.608	58.108	41.004	17.38
3203	PHE	CD1	41.729	58.330	40.223	17.66
3204	PHE	CD2	40.649	58.448	42.351	20.46
3205	PHE	CE1	42.902	58.849	40.752	17.85
3206	PHE	CE2	41.842	58.951	42.901	21.97
3207	PHE	CZ	42.980	59.145	42.099	19.00
3208	PHE	H	40.315	56.444	38.339	20.00
3209	PHE	HA	40.353	55.693	41.035	20.00
3210	PHE	1HB	38.539	57.656	41.135	20.00
3211	PHE	2HB	39.078	57.912	39.521	20.00
3212	PHE	HD1	41.687	58.093	39.172	20.00
3213	PHE	HD2	39.778	58.316	42.988	20.00
3214	PHE	HE1	43.761	58.990	40.117	20.00

3215	PHE	HE2	41.841	59.192	43.957	20.00
3216	PHE	HZ	43.888	59.517	42.548	20.00
3217	LYS	N	37.472	54.865	39.696	14.03
3218	LYS	CA	36.583	53.707	39.921	13.68
3219	LYS	C	37.382	52.381	40.226	13.76
3220	LYS	O	37.060	51.643	41.128	13.17
3221	LYS	CB	35.710	53.494	38.629	17.74
3222	LYS	CG	34.241	53.905	38.681	26.69
3223	LYS	CD	33.252	52.778	39.167	32.82
3224	LYS	CE	31.708	53.171	39.423	34.45
3225	LYS	NZ	30.586	52.149	39.327	39.18
3226	LYS	H	37.491	55.414	38.855	20.00
3227	LYS	HA	35.958	53.951	40.781	20.00
3228	LYS	1HB	35.782	52.475	38.241	20.00
3229	LYS	2HB	36.164	54.118	37.857	20.00
3230	LYS	1HG	34.004	54.112	37.648	20.00
3231	LYS	2HG	34.101	54.839	39.226	20.00
3232	LYS	1HD	33.656	52.326	40.073	20.00
3233	LYS	2HD	33.287	51.993	38.414	20.00
3234	LYS	1HE	31.446	53.975	38.749	20.00
3235	LYS	2HE	31.667	53.627	40.417	20.00
3236	LYS	1HZ	30.720	51.336	39.961	20.00
3237	LYS	2HZ	30.445	51.758	38.364	20.00
3238	LYS	3HZ	29.655	52.552	39.548	20.00
3239	VAL	N	38.441	52.045	39.435	13.89
3240	VAL	CA	39.117	50.767	39.646	11.86
3241	VAL	C	39.668	50.735	41.109	11.86
3242	VAL	O	39.382	49.808	41.856	11.98
3243	VAL	CB	40.222	50.455	38.595	12.00
3244	VAL	CG1	39.714	50.431	37.083	11.88
3245	VAL	CG2	40.882	49.143	38.956	12.37
3246	VAL	H	38.644	52.666	38.678	20.00
3247	VAL	HA	38.347	50.001	39.562	20.00
3248	VAL	HB	40.980	51.236	38.654	20.00
3249	VAL	1HG1	39.334	51.404	36.781	20.00
3250	VAL	2HG1	38.911	49.717	36.936	20.00
3251	VAL	3HG1	40.521	50.193	36.388	20.00
3252	VAL	1HG2	40.141	48.344	38.985	20.00
3253	VAL	2HG2	41.338	49.168	39.940	20.00
3254	VAL	3HG2	41.657	48.868	38.246	20.00
3255	ARG	N	40.409	51.870	41.447	12.93
3256	ARG	CA	40.873	52.261	42.832	14.48
3257	ARG	C	39.825	52.066	43.972	16.45
3258	ARG	O	39.966	51.141	44.744	17.22
3259	ARG	CB	41.467	53.625	42.820	13.76
3260	ARG	CG	42.889	53.536	42.265	12.22
3261	ARG	CD	43.652	54.811	42.463	13.67
3262	ARG	NE	45.033	54.629	42.060	15.68
3263	ARG	CZ	46.003	55.526	42.281	14.21
3264	ARG	NH1	45.760	56.603	42.913	12.91
3265	ARG	NH2	47.224	55.411	41.884	12.03
3266	ARG	H	40.563	52.500	40.699	20.00

3267	ARG	HA	41.629	51.519	43.075	20.00
3268	ARG	1HB	41.495	54.037	43.832	20.00
3269	ARG	2HB	40.831	54.268	42.232	20.00
3270	ARG	1HG	42.853	53.277	41.206	20.00
3271	ARG	2HG	43.451	52.741	42.750	20.00
3272	ARG	1HD	43.664	55.063	43.522	20.00
3273	ARG	2HD	43.212	55.649	41.915	20.00
3274	ARG	HE	45.320	53.862	41.467	20.00
3275	ARG	1HH1	46.502	57.215	43.201	20.00
3276	ARG	2HH1	44.822	56.812	43.169	20.00
3277	ARG	1HH2	47.930	56.047	42.164	20.00
3278	ARG	2HH2	47.472	54.665	41.247	20.00
3279	GLU	N	38.745	52.856	43.977	16.23
3280	GLU	CA	37.684	52.766	45.003	16.92
3281	GLU	C	37.252	51.348	45.300	16.63
3282	GLU	O	36.916	50.971	46.419	17.05
3283	GLU	CB	36.444	53.545	44.582	21.77
3284	GLU	CG	36.799	54.907	43.984	30.11
3285	GLU	CD	37.027	55.961	44.992	37.62
3286	GLU	OE1	36.553	57.060	44.734	42.75
3287	GLU	OE2	37.678	55.675	46.010	39.25
3288	GLU	H	38.672	53.569	43.277	20.00
3289	GLU	HA	38.104	53.180	45.920	20.00
3290	GLU	1HB	35.743	53.654	45.404	20.00
3291	GLU	2HB	35.911	53.001	43.806	20.00
3292	GLU	1HG	36.049	55.234	43.267	20.00
3293	GLU	2HG	37.756	54.964	43.507	20.00
3294	SER	N	37.245	50.596	44.208	16.50
3295	SER	CA	36.586	49.299	44.192	17.63
3296	SER	C	37.276	48.308	45.115	20.41
3297	SER	O	36.752	47.306	45.551	21.90
3298	SER	CB	36.543	48.757	42.749	14.84
3299	SER	OG	37.770	47.902	42.522	13.92
3300	SER	H	37.593	51.010	43.365	20.00
3301	SER	HA	35.572	49.436	44.561	20.00
3302	SER	1HB	36.155	49.519	42.003	20.00
3303	SER	2HB	35.639	48.112	42.750	20.00
3304	SER	HG	38.700	48.252	42.358	20.00
3305	GLY	N	38.524	48.565	45.371	20.72
3306	GLY	CA	39.194	47.651	46.288	20.75
3307	GLY	C	40.089	46.595	45.636	22.62
3308	GLY	O	40.792	45.813	46.284	25.75
3309	GLY	H	38.903	49.440	45.055	20.00
3310	GLY	1HA	38.508	47.150	46.966	20.00
3311	GLY	2HA	39.722	48.329	46.930	20.00
3312	SER	N	40.027	46.568	44.280	20.77
3313	SER	CA	40.726	45.501	43.613	20.37
3314	SER	C	42.153	45.729	43.531	22.30
3315	SER	O	42.854	44.771	43.336	22.94
3316	SER	CB	40.220	45.343	42.184	17.21
3317	SER	OG	38.756	45.469	42.138	16.17
3318	SER	H	39.321	47.129	43.860	20.00

3319	SER	HA	40.564	44.582	44.184	20.00
3320	SER	1HB	40.511	44.313	41.903	20.00
3321	SER	2HB	40.832	45.875	41.397	20.00
3322	SER	HG	38.200	46.170	42.594	20.00
3323	LEU	N	42.580	46.968	43.678	22.44
3324	LEU	CA	44.021	47.151	43.601	25.58
3325	LEU	C	44.758	46.978	44.971	29.18
3326	LEU	O	45.885	47.472	45.142	34.54
3327	LEU	CB	44.227	48.551	43.032	23.62
3328	LEU	CG	43.771	48.613	41.595	22.66
3329	LEU	CD1	44.790	47.909	40.682	23.63
3330	LEU	CD2	43.739	50.030	41.191	25.59
3331	LEU	H	41.920	47.692	43.869	20.00
3332	LEU	HA	44.457	46.425	42.916	20.00
3333	LEU	1HB	45.272	48.860	43.086	20.00
3334	LEU	2HB	43.668	49.264	43.642	20.00
3335	LEU	HG	42.768	48.203	41.473	20.00
3336	LEU	1HD1	44.838	46.837	40.861	20.00
3337	LEU	2HD1	45.797	48.314	40.814	20.00
3338	LEU	3HD1	44.523	48.057	39.636	20.00
3339	LEU	1HD2	44.730	50.484	41.260	20.00
3340	LEU	2HD2	43.082	50.610	41.825	20.00
3341	LEU	3HD2	43.390	50.156	40.166	20.00
3342	SER	N	44.047	46.362	45.949	27.88
3343	SER	CA	44.527	46.315	47.294	28.98
3344	SER	C	45.268	45.026	47.535	29.17
3345	SER	O	44.928	44.000	46.945	29.28
3346	SER	CB	43.294	46.473	48.203	29.56
3347	SER	OG	42.391	47.648	47.851	38.82
3348	SER	H	43.142	45.971	45.753	20.00
3349	SER	HA	45.282	47.090	47.412	20.00
3350	SER	1HB	43.680	46.480	49.240	20.00
3351	SER	2HB	42.704	45.533	48.129	20.00
3352	SER	HG	42.660	48.585	47.609	20.00
3353	PRO	N	46.350	45.122	48.386	28.99
3354	PRO	CA	47.235	44.009	48.606	28.15
3355	PRO	C	46.665	42.947	49.550	27.34
3356	PRO	O	47.292	41.932	49.843	28.43
3357	PRO	CB	48.430	44.664	49.261	29.14
3358	PRO	CG	47.828	45.786	50.081	28.91
3359	PRO	CD	46.762	46.306	49.144	28.77
3360	PRO	HA	47.507	43.522	47.670	20.00
3361	PRO	1HB	49.098	45.079	48.505	20.00
3362	PRO	2HB	49.021	43.976	49.861	20.00
3363	PRO	1HG	47.380	45.394	50.989	20.00
3364	PRO	2HG	48.563	46.532	50.377	20.00
3365	PRO	1HD	47.199	47.044	48.471	20.00
3366	PRO	2HD	45.931	46.753	49.695	20.00
3367	GLU	N	45.457	43.150	49.997	25.89
3368	GLU	CA	44.871	41.988	50.605	27.19
3369	GLU	C	44.368	41.012	49.552	26.00
3370	GLU	O	43.942	39.916	49.893	25.89

3371	GLU	CB	43.911	42.425	51.728	33.55
3372	GLU	CG	42.550	43.115	51.372	41.02
3373	GLU	CD	42.705	44.505	50.654	47.74
3374	GLU	OE1	43.847	45.031	50.685	49.25
3375	GLU	OE2	41.702	45.025	50.090	51.04
3376	GLU	H	44.923	43.947	49.758	20.00
3377	GLU	HA	45.628	41.417	51.145	20.00
3378	GLU	1HB	44.457	43.059	52.424	20.00
3379	GLU	2HB	43.665	41.517	52.278	20.00
3380	GLU	1HG	41.959	43.265	52.272	20.00
3381	GLU	2HG	41.958	42.466	50.731	20.00
3382	HIS	N	44.471	41.415	48.248	21.92
3383	HIS	CA	44.127	40.631	47.048	18.96
3384	HIS	C	45.367	40.200	46.240	17.83
3385	HIS	O	46.450	40.745	46.401	17.07
3386	HIS	CB	43.211	41.449	46.115	20.94
3387	HIS	CG	41.922	41.788	46.796	20.70
3388	HIS	ND1	41.464	43.035	47.020	22.42
3389	HIS	CD2	40.920	40.898	47.210	19.89
3390	HIS	CE1	40.213	42.908	47.536	18.97
3391	HIS	NE2	39.847	41.615	47.661	19.93
3392	HIS	H	44.691	42.370	48.072	20.00
3393	HIS	HA	43.622	39.722	47.371	20.00
3394	HIS	1HB	42.958	40.907	45.199	20.00
3395	HIS	2HB	43.680	42.390	45.807	20.00
3396	HIS	HD1	41.918	43.894	46.893	20.00
3397	HIS	HD2	41.004	39.819	47.163	20.00
3398	HIS	HE1	39.593	43.730	47.851	20.00
3399	GLY	N	45.184	39.221	45.302	16.31
3400	GLY	CA	46.302	39.054	44.354	14.07
3401	GLY	C	46.385	40.252	43.419	12.35
3402	GLY	O	45.650	41.217	43.559	13.46
3403	GLY	H	44.287	38.802	45.246	20.00
3404	GLY	1HA	46.107	38.168	43.769	20.00
3405	GLY	2HA	47.243	38.952	44.893	20.00
3406	PRO	N	47.313	40.254	42.476	11.56
3407	PRO	CA	47.457	41.398	41.621	13.06
3408	PRO	C	46.319	41.572	40.614	12.70
3409	PRO	O	45.791	40.570	40.113	13.68
3410	PRO	CB	48.793	41.186	40.861	11.82
3411	PRO	CG	49.194	39.809	41.186	12.42
3412	PRO	CD	48.405	39.318	42.377	11.92
3413	PRO	HA	47.521	42.314	42.213	20.00
3414	PRO	1HB	49.530	41.880	41.216	20.00
3415	PRO	2HB	48.701	41.370	39.795	20.00
3416	PRO	1HG	48.850	39.180	40.380	20.00
3417	PRO	2HG	50.270	39.657	41.272	20.00
3418	PRO	1HD	49.014	39.338	43.284	20.00
3419	PRO	2HD	48.052	38.297	42.234	20.00
3420	VAL	N	45.973	42.849	40.334	12.70
3421	VAL	CA	44.929	42.963	39.339	12.91
3422	VAL	C	45.483	42.510	37.953	13.19

3423	VAL	O	46.621	42.728	37.620	11.64
3424	VAL	CB	44.496	44.421	39.253	13.06
3425	VAL	CG1	43.349	44.731	38.248	14.25
3426	VAL	CG2	45.666	45.279	38.707	13.39
3427	VAL	H	46.382	43.579	40.884	20.00
3428	VAL	HA	44.101	42.315	39.632	20.00
3429	VAL	HB	44.216	44.757	40.258	20.00
3430	VAL	1HG1	42.439	44.202	38.530	20.00
3431	VAL	2HG1	43.570	44.460	37.215	20.00
3432	VAL	3HG1	43.120	45.801	38.259	20.00
3433	VAL	1HG2	45.922	45.076	37.665	20.00
3434	VAL	2HG2	46.576	45.157	39.298	20.00
3435	VAL	3HG2	45.433	46.341	38.734	20.00
3436	VAL	N	44.602	41.927	37.144	12.59
3437	VAL	CA	44.881	41.577	35.752	11.98
3438	VAL	C	44.531	42.778	34.849	12.38
3439	VAL	O	43.397	43.158	34.785	15.24
3440	VAL	CB	44.176	40.272	35.374	9.51
3441	VAL	CG1	44.743	39.059	36.135	9.49
3442	VAL	CG2	44.361	39.925	33.910	10.06
3443	VAL	H	43.709	41.713	37.540	20.00
3444	VAL	HA	45.954	41.413	35.671	20.00
3445	VAL	HB	43.115	40.379	35.597	20.00
3446	VAL	1HG1	44.479	39.140	37.183	20.00
3447	VAL	2HG1	45.824	38.965	36.047	20.00
3448	VAL	3HG1	44.325	38.113	35.792	20.00
3449	VAL	1HG2	45.410	39.826	33.635	20.00
3450	VAL	2HG2	43.899	40.660	33.252	20.00
3451	VAL	3HG2	43.873	38.976	33.702	20.00
3452	VAL	N	45.479	43.359	34.121	10.51
3453	VAL	CA	45.213	44.321	33.091	10.15
3454	VAL	C	45.520	43.549	31.813	11.07
3455	VAL	O	46.535	42.885	31.627	11.12
3456	VAL	CB	46.096	45.556	33.342	9.24
3457	VAL	CG1	46.058	45.910	34.877	8.57
3458	VAL	CG2	45.692	46.835	32.573	9.28
3459	VAL	H	46.407	43.018	34.253	20.00
3460	VAL	HA	44.159	44.590	33.110	20.00
3461	VAL	HB	47.120	45.295	33.080	20.00
3462	VAL	1HG1	46.514	45.136	35.496	20.00
3463	VAL	2HG1	45.048	46.086	35.240	20.00
3464	VAL	3HG1	46.642	46.804	35.079	20.00
3465	VAL	1HG2	44.720	47.202	32.917	20.00
3466	VAL	2HG2	45.588	46.664	31.520	20.00
3467	VAL	3HG2	46.421	47.627	32.738	20.00
3468	HIS	N	44.588	43.703	30.899	10.38
3469	HIS	CA	44.843	43.345	29.524	8.48
3470	HIS	C	44.257	44.454	28.566	10.06
3471	HIS	O	43.285	45.158	28.830	9.96
3472	HIS	CB	44.287	41.924	29.313	8.91
3473	HIS	CG	42.824	41.948	28.937	8.64
3474	HIS	ND1	42.370	41.918	27.656	7.44

3475	HIS	CD2	41.783	41.815	29.793	8.51
3476	HIS	CE1	41.082	41.735	27.708	9.19
3477	HIS	NE2	40.730	41.677	28.984	11.46
3478	HIS	H	43.749	44.180	31.164	20.00
3479	HIS	HA	45.921	43.222	29.367	20.00
3480	HIS	1HB	44.424	41.327	30.215	20.00
3481	HIS	2HB	44.812	41.427	28.502	20.00
3482	HIS	HD1	42.926	41.960	26.851	20.00
3483	HIS	HD2	41.793	41.781	30.873	20.00
3484	HIS	HE1	40.391	41.585	26.885	20.00
3485	CYS	N	44.901	44.539	27.410	10.31
3486	CYS	CA	44.335	45.149	26.196	8.62
3487	CYS	C	44.351	44.032	25.182	9.41
3488	CYS	O	44.133	42.849	25.460	9.11
3489	CYS	CB	45.153	46.362	25.753	9.94
3490	CYS	SG	47.021	46.150	25.889	10.94
3491	CYS	H	45.698	43.931	27.402	20.00
3492	CYS	HA	43.311	45.451	26.378	20.00
3493	CYS	1HB	44.769	47.265	26.233	20.00
3494	CYS	2HB	44.846	46.673	24.780	20.00
3495	CYS	HG	47.564	46.018	24.675	20.00
3496	SER	N	44.663	44.316	23.984	9.15
3497	SER	CA	44.722	43.139	23.130	8.78
3498	SER	C	46.105	42.359	23.239	8.55
3499	SER	O	46.217	41.128	23.347	8.15
3500	SER	CB	44.389	43.699	21.683	7.93
3501	SER	OG	44.662	42.684	20.631	8.26
3502	SER	H	44.850	45.208	23.621	20.00
3503	SER	HA	43.891	42.482	23.434	20.00
3504	SER	1HB	45.102	44.543	21.547	20.00
3505	SER	2HB	43.440	44.339	21.661	20.00
3506	SER	HG	44.215	41.792	20.609	20.00
3507	ALA	N	47.234	43.166	23.239	8.61
3508	ALA	CA	48.571	42.556	23.451	7.66
3509	ALA	C	49.048	42.526	24.949	8.82
3510	ALA	O	49.906	41.719	25.386	11.75
3511	ALA	CB	49.495	43.448	22.703	7.00
3512	ALA	H	47.101	44.074	22.832	20.00
3513	ALA	HA	48.580	41.555	23.021	20.00
3514	ALA	1HB	49.449	44.478	23.062	20.00
3515	ALA	2HB	49.221	43.481	21.650	20.00
3516	ALA	3HB	50.531	43.112	22.754	20.00
3517	GLY	N	48.451	43.474	25.731	8.66
3518	GLY	CA	48.838	43.523	27.166	8.32
3519	GLY	C	50.020	44.449	27.521	9.76
3520	GLY	O	50.750	44.217	28.493	10.12
3521	GLY	H	47.716	43.998	25.323	20.00
3522	GLY	1HA	49.118	42.517	27.472	20.00
3523	GLY	2HA	47.962	43.705	27.760	20.00
3524	ILE	N	50.209	45.476	26.649	11.14
3525	ILE	CA	51.393	46.367	26.588	12.07
3526	ILE	C	51.104	47.859	26.189	10.76

3527	ILE	O	51.483	48.766	26.906	12.85
3528	ILE	CB	52.535	45.757	25.705	8.68
3529	ILE	CG1	52.223	45.596	24.220	9.17
3530	ILE	CG2	52.925	44.361	26.249	8.98
3531	ILE	CD1	53.481	45.306	23.388	7.46
3532	ILE	H	49.535	45.515	25.921	20.00
3533	ILE	HA	51.746	46.417	27.621	20.00
3534	ILE	HB	53.406	46.400	25.807	20.00
3535	ILE	1HG1	51.822	46.511	23.805	20.00
3536	ILE	2HG1	51.482	44.821	24.044	20.00
3537	ILE	1HG2	52.130	43.636	26.107	20.00
3538	ILE	2HG2	53.153	44.435	27.313	20.00
3539	ILE	3HG2	53.807	43.971	25.748	20.00
3540	ILE	1HD1	53.909	44.318	23.568	20.00
3541	ILE	2HD1	54.265	46.026	23.602	20.00
3542	ILE	3HD1	53.262	45.368	22.319	20.00
3543	GLY	N	50.417	48.135	25.062	10.38
3544	GLY	CA	50.161	49.536	24.720	9.10
3545	GLY	C	49.289	50.270	25.787	10.90
3546	GLY	O	49.707	51.067	26.645	10.20
3547	GLY	H	50.328	47.389	24.405	20.00
3548	GLY	1HA	49.709	49.560	23.740	20.00
3549	GLY	2HA	51.112	50.049	24.648	20.00
3550	ARG	N	48.015	49.955	25.638	11.01
3551	ARG	CA	47.000	50.422	26.563	10.63
3552	ARG	C	47.250	49.944	28.078	10.18
3553	ARG	O	47.128	50.731	28.993	10.97
3554	ARG	CB	45.607	50.070	26.013	9.12
3555	ARG	CG	45.144	50.880	24.746	9.78
3556	ARG	CD	43.773	50.426	24.185	7.58
3557	ARG	NE	44.049	49.233	23.356	8.89
3558	ARG	CZ	43.196	48.582	22.597	9.55
3559	ARG	NH1	41.972	48.921	22.463	10.16
3560	ARG	NH2	43.540	47.568	21.873	9.68
3561	ARG	H	47.708	49.447	24.827	20.00
3562	ARG	HA	47.003	51.506	26.576	20.00
3563	ARG	1HB	44.861	50.223	26.789	20.00
3564	ARG	2HB	45.634	49.021	25.746	20.00
3565	ARG	1HG	45.900	50.827	23.957	20.00
3566	ARG	2HG	45.132	51.924	25.011	20.00
3567	ARG	1HD	43.364	51.196	23.526	20.00
3568	ARG	2HD	43.068	50.217	24.981	20.00
3569	ARG	HE	45.007	48.990	23.182	20.00
3570	ARG	1HH1	41.396	48.399	21.816	20.00
3571	ARG	2HH1	41.590	49.702	22.945	20.00
3572	ARG	1HH2	42.793	47.113	21.366	20.00
3573	ARG	2HH2	44.482	47.294	21.669	20.00
3574	SER	N	47.594	48.689	28.346	10.07
3575	SER	CA	47.913	48.208	29.693	8.26
3576	SER	C	49.065	48.962	30.267	10.19
3577	SER	O	48.901	49.340	31.398	10.34
3578	SER	CB	48.033	46.638	29.836	8.89

3579	SER	OG	46.922	45.809	29.211	11.05
3580	SER	H	47.665	48.073	27.569	20.00
3581	SER	HA	47.089	48.557	30.322	20.00
3582	SER	1HB	48.069	46.443	30.939	20.00
3583	SER	2HB	49.068	46.298	29.561	20.00
3584	SER	HG	46.279	46.160	28.550	20.00
3585	GLY	N	50.182	49.229	29.505	10.44
3586	GLY	CA	51.325	49.953	30.078	8.60
3587	GLY	C	50.896	51.373	30.405	9.62
3588	GLY	O	51.139	51.879	31.498	11.83
3589	GLY	H	50.224	48.899	28.558	20.00
3590	GLY	1HA	52.103	49.991	29.311	20.00
3591	GLY	2HA	51.649	49.439	30.989	20.00
3592	THR	N	50.155	52.015	29.454	11.37
3593	THR	CA	49.632	53.367	29.813	10.02
3594	THR	C	48.846	53.501	31.196	11.10
3595	THR	O	49.111	54.330	32.043	9.82
3596	THR	CB	48.658	53.726	28.649	9.53
3597	THR	OG1	49.394	53.774	27.401	10.14
3598	THR	CG2	48.212	55.179	28.705	8.73
3599	THR	H	50.061	51.610	28.544	20.00
3600	THR	HA	50.475	54.060	29.842	20.00
3601	THR	HB	47.638	53.223	28.821	20.00
3602	THR	HG1	49.688	52.952	26.910	20.00
3603	THR	1HG2	49.090	55.745	28.772	20.00
3604	THR	2HG2	47.611	55.422	29.584	20.00
3605	THR	3HG2	47.726	55.537	27.806	20.00
3606	PHE	N	47.836	52.592	31.360	9.10
3607	PHE	CA	46.998	52.422	32.513	10.60
3608	PHE	C	47.763	52.282	33.849	10.58
3609	PHE	O	47.468	53.018	34.785	11.24
3610	PHE	CB	46.107	51.169	32.361	8.88
3611	PHE	CG	45.222	51.035	33.635	9.58
3612	PHE	CD1	43.998	51.687	33.724	11.54
3613	PHE	CD2	45.625	50.250	34.736	11.23
3614	PHE	CE1	43.198	51.577	34.840	6.44
3615	PHE	CE2	44.807	50.110	35.884	9.94
3616	PHE	CZ	43.575	50.768	35.919	6.47
3617	PHE	H	47.740	51.934	30.607	20.00
3618	PHE	HA	46.395	53.324	32.576	20.00
3619	PHE	1HB	46.680	50.256	32.197	20.00
3620	PHE	2HB	45.487	51.288	31.473	20.00
3621	PHE	HD1	43.670	52.276	32.877	20.00
3622	PHE	HD2	46.584	49.739	34.711	20.00
3623	PHE	HE1	42.263	52.121	34.876	20.00
3624	PHE	HE2	45.155	49.525	36.733	20.00
3625	PHE	HZ	42.947	50.692	36.793	20.00
3626	CYS	N	48.703	51.295	33.817	10.70
3627	CYS	CA	49.631	50.947	34.885	10.02
3628	CYS	C	50.699	52.006	35.192	10.89
3629	CYS	O	51.065	52.292	36.335	12.32
3630	CYS	CB	50.376	49.689	34.433	12.17

3631	CYS	SG	49.243	48.345	34.666	15.41
3632	CYS	H	48.709	50.767	32.964	20.00
3633	CYS	HA	49.055	50.755	35.790	20.00
3634	CYS	1HB	51.208	49.519	35.117	20.00
3635	CYS	2HB	50.793	49.726	33.426	20.00
3636	CYS	HG	48.768	48.009	33.459	20.00
3637	LEU	N	51.226	52.596	34.112	10.01
3638	LEU	CA	52.185	53.673	34.273	10.37
3639	LEU	C	51.674	54.833	35.143	10.12
3640	LEU	O	52.319	55.313	36.051	9.30
3641	LEU	CB	52.734	54.180	32.895	9.12
3642	LEU	CG	53.780	55.327	33.205	11.23
3643	LEU	CD1	54.197	56.096	31.977	11.32
3644	LEU	CD2	55.004	54.815	34.036	11.96
3645	LEU	H	50.866	52.331	33.223	20.00
3646	LEU	HA	53.005	53.241	34.825	20.00
3647	LEU	1HB	51.930	54.585	32.286	20.00
3648	LEU	2HB	53.201	53.374	32.332	20.00
3649	LEU	HG	53.317	56.100	33.819	20.00
3650	LEU	1HD1	53.342	56.567	31.505	20.00
3651	LEU	2HD1	54.636	55.435	31.232	20.00
3652	LEU	3HD1	54.937	56.849	32.198	20.00
3653	LEU	1HD2	55.470	53.966	33.544	20.00
3654	LEU	2HD2	54.680	54.473	35.013	20.00
3655	LEU	3HD2	55.757	55.589	34.178	20.00
3656	ALA	N	50.511	55.296	34.725	10.91
3657	ALA	CA	49.836	56.419	35.284	10.80
3658	ALA	C	49.353	56.116	36.768	11.33
3659	ALA	O	49.659	56.874	37.671	10.76
3660	ALA	CB	48.789	56.860	34.272	7.83
3661	ALA	H	50.129	54.843	33.918	20.00
3662	ALA	HA	50.597	57.196	35.359	20.00
3663	ALA	1HB	48.087	56.053	34.063	20.00
3664	ALA	2HB	49.263	57.110	33.316	20.00
3665	ALA	3HB	48.242	57.733	34.616	20.00
3666	ASP	N	48.709	54.939	37.028	11.75
3667	ASP	CA	48.530	54.419	38.415	11.91
3668	ASP	C	49.770	54.521	39.379	11.55
3669	ASP	O	49.711	55.168	40.421	11.95
3670	ASP	CB	47.928	52.991	38.350	10.16
3671	ASP	CG	47.508	52.440	39.753	13.48
3672	ASP	OD1	46.984	53.154	40.612	12.31
3673	ASP	OD2	47.716	51.287	40.031	12.63
3674	ASP	H	48.369	54.406	36.245	20.00
3675	ASP	HA	47.781	55.068	38.858	20.00
3676	ASP	1HB	48.599	52.290	37.857	20.00
3677	ASP	2HB	47.011	53.008	37.763	20.00
3678	THR	N	50.869	53.897	38.951	10.97
3679	THR	CA	52.060	53.792	39.783	11.02
3680	THR	C	52.733	55.095	39.943	11.79
3681	THR	O	53.143	55.434	41.062	11.99
3682	THR	CB	53.122	52.827	39.159	11.07

3683	THR	OG1	52.653	51.451	38.973	11.80
3684	THR	CG2	54.351	52.594	40.065	10.36
3685	THR	H	50.727	53.360	38.110	20.00
3686	THR	HA	51.787	53.543	40.811	20.00
3687	THR	HB	53.646	53.341	38.290	20.00
3688	THR	HG1	51.720	51.234	38.657	20.00
3689	THR	1HG2	54.046	52.144	41.006	20.00
3690	THR	2HG2	54.884	53.516	40.274	20.00
3691	THR	3HG2	55.051	51.906	39.588	20.00
3692	CYS	N	52.728	55.872	38.863	10.65
3693	CYS	CA	53.207	57.210	39.137	10.63
3694	CYS	C	52.322	58.003	40.111	12.96
3695	CYS	O	52.866	58.826	40.820	13.56
3696	CYS	CB	53.409	58.056	37.880	10.48
3697	CYS	SG	54.835	57.579	36.906	13.42
3698	CYS	H	52.373	55.549	37.978	20.00
3699	CYS	HA	54.197	57.134	39.592	20.00
3700	CYS	1HB	53.582	59.091	38.184	20.00
3701	CYS	2HB	52.512	58.066	37.258	20.00
3702	CYS	HG	54.517	56.537	36.129	20.00
3703	LEU	N	50.996	57.761	40.200	10.64
3704	LEU	CA	50.209	58.546	41.149	11.23
3705	LEU	C	50.345	57.934	42.558	12.65
3706	LEU	O	50.250	58.570	43.589	14.44
3707	LEU	CB	48.712	58.588	40.748	9.49
3708	LEU	CG	48.459	59.449	39.550	8.57
3709	LEU	CD1	48.546	60.918	39.903	10.68
3710	LEU	CD2	47.149	59.075	38.926	11.48
3711	LEU	H	50.585	57.122	39.545	20.00
3712	LEU	HA	50.594	59.563	41.168	20.00
3713	LEU	1HB	48.112	58.972	41.572	20.00
3714	LEU	2HB	48.360	57.578	40.552	20.00
3715	LEU	HG	49.224	59.256	38.808	20.00
3716	LEU	1HD1	49.555	61.220	40.186	20.00
3717	LEU	2HD1	47.884	61.189	40.720	20.00
3718	LEU	3HD1	48.268	61.545	39.055	20.00
3719	LEU	1HD2	46.315	59.278	39.602	20.00
3720	LEU	2HD2	47.126	58.022	38.642	20.00
3721	LEU	3HD2	46.963	59.659	38.023	20.00
3722	LEU	N	50.587	56.660	42.564	13.24
3723	LEU	CA	50.835	56.004	43.863	12.90
3724	LEU	C	52.190	56.454	44.611	13.36
3725	LEU	O	52.395	56.408	45.830	15.00
3726	LEU	CB	50.904	54.505	43.469	12.90
3727	LEU	CG	49.835	53.569	43.939	17.31
3728	LEU	CD1	49.263	53.990	45.326	17.90
3729	LEU	CD2	50.526	52.220	43.957	17.91
3730	LEU	H	50.646	56.184	41.684	20.00
3731	LEU	HA	49.999	56.251	44.523	20.00
3732	LEU	1HB	51.908	54.136	43.644	20.00
3733	LEU	2HB	50.832	54.426	42.388	20.00
3734	LEU	HG	49.006	53.536	43.238	20.00

3735	LEU	1HD1	48.585	54.836	45.275	20.00
3736	LEU	2HD1	50.070	54.266	46.010	20.00
3737	LEU	3HD1	48.730	53.181	45.816	20.00
3738	LEU	1HD2	51.425	52.244	44.573	20.00
3739	LEU	2HD2	50.823	51.905	42.956	20.00
3740	LEU	3HD2	49.881	51.463	44.393	20.00
3741	LEU	N	53.129	56.820	43.760	14.06
3742	LEU	CA	54.476	57.023	44.220	15.83
3743	LEU	C	54.440	58.400	44.768	15.86
3744	LEU	O	54.749	58.682	45.911	15.48
3745	LEU	CB	55.357	56.970	42.985	15.91
3746	LEU	CG	56.668	56.200	43.023	18.29
3747	LEU	CD1	56.873	55.755	41.585	20.36
3748	LEU	CD2	56.800	55.028	43.983	16.23
3749	LEU	H	52.886	56.679	42.799	20.00
3750	LEU	HA	54.733	56.275	44.971	20.00
3751	LEU	1HB	55.586	57.948	42.562	20.00
3752	LEU	2HB	54.761	56.546	42.184	20.00
3753	LEU	HG	57.472	56.891	43.272	20.00
3754	LEU	1HD1	56.867	56.632	40.928	20.00
3755	LEU	2HD1	56.101	55.069	41.240	20.00
3756	LEU	3HD1	57.836	55.256	41.439	20.00
3757	LEU	1HD2	55.882	54.460	43.936	20.00
3758	LEU	2HD2	56.954	55.352	45.011	20.00
3759	LEU	3HD2	57.613	54.361	43.694	20.00
3760	MET	N	53.976	59.242	43.877	14.06
3761	MET	CA	53.624	60.606	44.191	16.10
3762	MET	C	52.765	60.733	45.517	18.37
3763	MET	O	53.079	61.547	46.384	17.82
3764	MET	CB	53.022	61.097	42.848	17.90
3765	MET	CG	52.600	62.534	42.880	22.88
3766	MET	SD	52.133	63.122	41.275	27.93
3767	MET	CE	53.674	62.882	40.484	21.01
3768	MET	H	53.802	58.889	42.947	20.00
3769	MET	HA	54.574	61.137	44.355	20.00
3770	MET	1HB	52.142	60.514	42.589	20.00
3771	MET	2HB	53.726	60.932	42.040	20.00
3772	MET	1HG	53.414	63.117	43.298	20.00
3773	MET	2HG	51.765	62.692	43.563	20.00
3774	MET	1HE	53.737	61.868	40.089	20.00
3775	MET	2HE	54.533	63.102	41.116	20.00
3776	MET	3HE	53.709	63.582	39.649	20.00
3777	ASP	N	51.796	59.845	45.706	17.66
3778	ASP	CA	51.046	59.817	46.959	18.72
3779	ASP	C	51.866	59.517	48.249	20.72
3780	ASP	O	51.506	60.010	49.317	18.46
3781	ASP	CB	49.865	58.833	46.789	15.77
3782	ASP	CG	48.692	59.223	47.720	15.78
3783	ASP	OD1	47.921	60.098	47.335	15.30
3784	ASP	OD2	48.573	58.745	48.849	12.03
3785	ASP	H	51.489	59.265	44.954	20.00
3786	ASP	HA	50.641	60.814	47.092	20.00

3787	ASP	1HB	50.143	57.792	46.991	20.00
3788	ASP	2HB	49.523	58.841	45.757	20.00
3789	LYS	N	52.983	58.760	48.131	22.67
3790	LYS	CA	53.674	58.145	49.290	26.79
3791	LYS	C	54.931	58.920	49.795	27.91
3792	LYS	O	55.952	58.446	50.319	27.25
3793	LYS	CB	53.901	56.634	49.079	31.63
3794	LYS	CG	55.221	56.174	48.432	36.21
3795	LYS	CD	55.564	54.732	48.920	41.15
3796	LYS	CE	54.502	53.672	48.501	45.83
3797	LYS	NZ	54.382	52.509	49.411	48.52
3798	LYS	H	53.168	58.421	47.202	20.00
3799	LYS	HA	52.971	58.231	50.127	20.00
3800	LYS	1HB	53.037	56.222	48.565	20.00
3801	LYS	2HB	53.878	56.200	50.076	20.00
3802	LYS	1HG	56.072	56.800	48.691	20.00
3803	LYS	2HG	55.142	56.208	47.346	20.00
3804	LYS	1HD	55.694	54.725	50.001	20.00
3805	LYS	2HD	56.528	54.416	48.507	20.00
3806	LYS	1HE	54.738	53.304	47.496	20.00
3807	LYS	2HE	53.519	54.136	48.398	20.00
3808	LYS	1HZ	54.131	52.810	50.372	20.00
3809	LYS	2HZ	55.273	51.969	49.417	20.00
3810	LYS	3HZ	53.633	51.882	49.045	20.00
3811	ARG	N	54.783	60.192	49.561	29.18
3812	ARG	CA	55.920	61.072	49.744	30.25
3813	ARG	C	55.412	62.476	49.597	28.51
3814	ARG	O	55.983	63.400	50.172	29.83
3815	ARG	CB	57.138	60.726	48.833	35.96
3816	ARG	CG	56.825	60.702	47.353	35.60
3817	ARG	CD	57.971	60.140	46.489	39.72
3818	ARG	NE	58.346	58.740	46.746	44.72
3819	ARG	CZ	59.252	58.052	45.985	49.49
3820	ARG	NH1	59.736	58.571	44.823	46.55
3821	ARG	NH2	59.631	56.831	46.444	54.27
3822	ARG	H	53.921	60.398	49.096	20.00
3823	ARG	HA	56.222	60.959	50.792	20.00
3824	ARG	1HB	57.517	59.753	49.136	20.00
3825	ARG	2HB	57.954	61.419	49.015	20.00
3826	ARG	1HG	56.572	61.699	46.997	20.00
3827	ARG	2HG	55.957	60.080	47.195	20.00
3828	ARG	1HD	58.897	60.700	46.658	20.00
3829	ARG	2HD	57.668	60.138	45.441	20.00
3830	ARG	HE	57.974	58.277	47.547	20.00
3831	ARG	1HH1	60.317	57.968	44.264	20.00
3832	ARG	2HH1	59.524	59.501	44.534	20.00
3833	ARG	1HH2	60.241	56.297	45.852	20.00
3834	ARG	2HH2	59.320	56.463	47.308	20.00
3835	LYS	N	54.299	62.635	48.843	24.03
3836	LYS	CA	53.709	63.975	48.683	22.66
3837	LYS	C	54.836	65.076	48.313	22.19
3838	LYS	O	54.746	66.296	48.531	22.54

3839	LYS	CB	52.828	64.382	49.905	23.45
3840	LYS	CG	51.703	63.412	50.390	20.10
3841	LYS	CD	50.532	63.202	49.448	20.71
3842	LYS	CE	49.505	62.232	50.059	17.94
3843	LYS	NZ	48.450	61.958	49.071	27.72
3844	LYS	H	53.968	61.880	48.276	20.00
3845	LYS	HA	53.071	63.873	47.806	20.00
3846	LYS	1HB	52.363	65.342	49.684	20.00
3847	LYS	2HB	53.494	64.560	50.747	20.00
3848	LYS	1HG	51.304	63.828	51.315	20.00
3849	LYS	2HG	52.136	62.454	50.672	20.00
3850	LYS	1HD	50.884	62.812	48.489	20.00
3851	LYS	2HD	50.052	64.161	49.235	20.00
3852	LYS	1HE	49.049	62.670	50.950	20.00
3853	LYS	2HE	49.952	61.283	50.363	20.00
3854	LYS	1HZ	48.810	61.313	48.331	20.00
3855	LYS	2HZ	48.109	62.817	48.578	20.00
3856	LYS	3HZ	47.647	61.409	49.432	20.00
3857	ASP	N	55.889	64.482	47.680	21.48
3858	ASP	CA	56.806	65.251	46.882	22.85
3859	ASP	C	56.543	64.944	45.345	21.41
3860	ASP	O	57.198	64.103	44.713	21.48
3861	ASP	CB	58.216	64.968	47.416	25.58
3862	ASP	CG	59.244	65.767	46.566	29.64
3863	ASP	OD1	58.862	66.819	45.964	31.77
3864	ASP	OD2	60.408	65.344	46.549	30.41
3865	ASP	H	56.060	63.508	47.768	20.00
3866	ASP	HA	56.609	66.305	47.057	20.00
3867	ASP	1HB	58.465	63.918	47.556	20.00
3868	ASP	2HB	58.277	65.369	48.429	20.00
3869	PRO	N	55.539	65.638	44.744	20.58
3870	PRO	CA	55.308	65.416	43.295	22.04
3871	PRO	C	56.569	65.307	42.347	24.22
3872	PRO	O	56.572	64.547	41.372	22.77
3873	PRO	CB	54.441	66.653	42.852	23.82
3874	PRO	CG	53.958	67.350	44.156	22.76
3875	PRO	CD	54.861	66.824	45.284	22.17
3876	PRO	HA	54.784	64.489	43.157	20.00
3877	PRO	1HB	53.643	66.360	42.176	20.00
3878	PRO	2HB	55.022	67.367	42.285	20.00
3879	PRO	1HG	53.966	68.430	44.056	20.00
3880	PRO	2HG	52.945	67.022	44.344	20.00
3881	PRO	1HD	54.292	66.563	46.162	20.00
3882	PRO	2HD	55.589	67.586	45.557	20.00
3883	SER	N	57.644	66.017	42.810	26.49
3884	SER	CA	58.744	66.328	41.960	29.21
3885	SER	C	59.732	65.218	41.913	28.16
3886	SER	O	60.301	64.849	40.890	30.98
3887	SER	CB	59.304	67.616	42.594	32.36
3888	SER	OG	58.637	68.913	42.285	37.57
3889	SER	H	57.630	66.394	43.738	20.00
3890	SER	HA	58.429	66.385	40.908	20.00

3891	SER	1HB	60.351	67.694	42.232	20.00
3892	SER	2HB	59.521	67.454	43.682	20.00
3893	SER	HG	57.670	69.067	42.060	20.00
3894	SER	N	59.925	64.613	43.043	25.94
3895	SER	CA	60.809	63.466	42.969	23.97
3896	SER	C	60.407	62.308	41.968	23.07
3897	SER	O	61.251	61.419	41.868	23.41
3898	SER	CB	60.695	62.845	44.395	24.53
3899	SER	OG	59.325	62.461	44.856	26.18
3900	SER	H	59.459	64.900	43.888	20.00
3901	SER	HA	61.810	63.811	42.723	20.00
3902	SER	1HB	61.331	63.448	45.113	20.00
3903	SER	2HB	61.358	61.949	44.388	20.00
3904	SER	HG	58.514	63.013	44.586	20.00
3905	VAL	N	59.176	62.231	41.306	22.45
3906	VAL	CA	58.834	61.027	40.461	21.20
3907	VAL	C	59.182	61.249	38.947	21.26
3908	VAL	O	58.675	62.163	38.320	22.49
3909	VAL	CB	57.391	60.434	40.620	22.58
3910	VAL	CG1	56.451	60.386	39.363	20.76
3911	VAL	CG2	56.695	61.029	41.828	17.17
3912	VAL	H	58.588	63.040	41.291	20.00
3913	VAL	HA	59.500	60.233	40.807	20.00
3914	VAL	HB	57.535	59.380	40.863	20.00
3915	VAL	1HG1	56.888	59.787	38.559	20.00
3916	VAL	2HG1	56.252	61.381	38.973	20.00
3917	VAL	3HG1	55.488	59.919	39.577	20.00
3918	VAL	1HG2	56.539	62.101	41.733	20.00
3919	VAL	2HG2	57.252	60.803	42.729	20.00
3920	VAL	3HG2	55.729	60.556	41.956	20.00
3921	ASP	N	60.034	60.370	38.393	19.92
3922	ASP	CA	60.422	60.486	37.014	19.98
3923	ASP	C	59.593	59.489	36.190	17.61
3924	ASP	O	59.810	58.291	36.270	18.51
3925	ASP	CB	61.968	60.298	36.922	21.39
3926	ASP	CG	62.632	60.452	35.517	25.31
3927	ASP	OD1	62.006	60.671	34.458	23.58
3928	ASP	OD2	63.846	60.336	35.498	32.08
3929	ASP	H	60.462	59.701	38.992	20.00
3930	ASP	HA	60.181	61.487	36.644	20.00
3931	ASP	1HB	62.267	59.369	37.393	20.00
3932	ASP	2HB	62.408	61.078	37.534	20.00
3933	ILE	N	58.641	60.060	35.429	18.00
3934	ILE	CA	57.715	59.212	34.684	16.17
3935	ILE	C	58.457	58.121	33.908	16.20
3936	ILE	O	58.158	56.962	33.989	16.71
3937	ILE	CB	56.682	60.059	33.831	18.69
3938	ILE	CG1	55.862	61.009	34.788	20.07
3939	ILE	CG2	55.633	59.144	33.082	16.13
3940	ILE	CD1	54.494	61.498	34.162	22.35
3941	ILE	H	58.643	61.059	35.410	20.00
3942	ILE	HA	57.154	58.675	35.450	20.00

3943	ILE	HB	57.226	60.649	33.091	20.00
3944	ILE	1HG1	56.474	61.858	35.081	20.00
3945	ILE	2HG1	55.628	60.471	35.709	20.00
3946	ILE	1HG2	55.008	58.573	33.774	20.00
3947	ILE	2HG2	56.178	58.446	32.443	20.00
3948	ILE	3HG2	54.982	59.699	32.406	20.00
3949	ILE	1HD1	53.818	60.694	33.876	20.00
3950	ILE	2HD1	54.710	62.086	33.280	20.00
3951	ILE	3HD1	53.924	62.104	34.865	20.00
3952	LYS	N	59.488	58.562	33.158	15.61
3953	LYS	CA	60.319	57.703	32.288	16.12
3954	LYS	C	61.173	56.727	33.130	15.62
3955	LYS	O	61.228	55.568	32.799	15.12
3956	LYS	CB	61.147	58.457	31.166	18.84
3957	LYS	CG	60.600	59.764	30.558	31.31
3958	LYS	CD	61.795	60.577	29.985	37.73
3959	LYS	CE	62.746	61.132	31.087	43.40
3960	LYS	NZ	62.754	62.577	31.255	47.06
3961	LYS	H	59.666	59.540	33.256	20.00
3962	LYS	HA	59.593	57.072	31.780	20.00
3963	LYS	1HB	61.394	57.754	30.371	20.00
3964	LYS	2HB	62.114	58.664	31.609	20.00
3965	LYS	1HG	60.123	60.303	31.374	20.00
3966	LYS	2HG	59.834	59.586	29.806	20.00
3967	LYS	1HD	61.613	61.325	29.225	20.00
3968	LYS	2HD	62.379	59.879	29.384	20.00
3969	LYS	1HE	63.770	60.795	30.916	20.00
3970	LYS	2HE	62.462	60.714	32.058	20.00
3971	LYS	1HZ	61.799	62.973	31.456	20.00
3972	LYS	2HZ	63.031	63.140	30.419	20.00
3973	LYS	3HZ	63.326	62.866	32.070	20.00
3974	LYS	N	61.763	57.189	34.225	16.19
3975	LYS	CA	62.257	56.242	35.200	17.17
3976	LYS	C	61.293	55.010	35.671	15.81
3977	LYS	O	61.750	53.857	35.780	13.38
3978	LYS	CB	62.721	57.021	36.420	21.47
3979	LYS	CG	63.685	56.179	37.285	26.41
3980	LYS	CD	64.794	57.072	37.807	32.75
3981	LYS	CE	65.626	57.849	36.734	37.01
3982	LYS	NZ	67.041	58.078	37.149	41.44
3983	LYS	H	61.705	58.168	34.443	20.00
3984	LYS	HA	63.127	55.786	34.726	20.00
3985	LYS	1HB	61.887	57.362	37.030	20.00
3986	LYS	2HB	63.231	57.909	36.056	20.00
3987	LYS	1HG	64.127	55.380	36.694	20.00
3988	LYS	2HG	63.149	55.685	38.097	20.00
3989	LYS	1HD	65.457	56.465	38.425	20.00
3990	LYS	2HD	64.355	57.817	38.475	20.00
3991	LYS	1HE	65.173	58.818	36.541	20.00
3992	LYS	2HE	65.625	57.311	35.781	20.00
3993	LYS	1HZ	67.519	57.178	37.364	20.00
3994	LYS	2HZ	67.048	58.692	37.990	20.00

3995	LYS	3HZ	67.545	58.575	36.382	20.00
3996	VAL	N	59.985	55.323	35.959	15.38
3997	VAL	CA	59.007	54.265	36.251	13.40
3998	VAL	C	58.622	53.424	35.039	12.42
3999	VAL	O	58.570	52.215	35.094	12.19
4000	VAL	CB	57.954	54.563	37.383	17.62
4001	VAL	CG1	56.568	53.984	37.220	13.70
4002	VAL	CG2	57.966	55.998	37.910	14.26
4003	VAL	H	59.750	56.303	35.924	20.00
4004	VAL	HA	59.627	53.531	36.757	20.00
4005	VAL	HB	58.323	54.004	38.246	20.00
4006	VAL	1HG1	56.577	52.930	36.941	20.00
4007	VAL	2HG1	56.042	54.545	36.459	20.00
4008	VAL	3HG1	55.990	54.074	38.141	20.00
4009	VAL	1HG2	57.755	56.693	37.096	20.00
4010	VAL	2HG2	58.937	56.269	38.321	20.00
4011	VAL	3HG2	57.210	56.147	38.681	20.00
4012	LEU	N	58.433	54.033	33.899	11.53
4013	LEU	CA	58.144	53.234	32.728	12.42
4014	LEU	C	59.278	52.236	32.445	11.91
4015	LEU	O	59.058	51.051	32.366	10.65
4016	LEU	CB	57.743	54.157	31.624	12.94
4017	LEU	CG	57.326	53.410	30.304	14.51
4018	LEU	CD1	57.086	54.408	29.182	14.86
4019	LEU	CD2	56.160	52.386	30.503	12.64
4020	LEU	H	58.437	55.031	33.911	20.00
4021	LEU	HA	57.258	52.666	32.990	20.00
4022	LEU	1HB	58.593	54.808	31.418	20.00
4023	LEU	2HB	56.941	54.822	31.950	20.00
4024	LEU	HG	58.192	52.818	30.000	20.00
4025	LEU	1HD1	57.963	55.014	29.049	20.00
4026	LEU	2HD1	56.240	55.060	29.390	20.00
4027	LEU	3HD1	56.896	53.878	28.248	20.00
4028	LEU	1HD2	55.276	52.909	30.864	20.00
4029	LEU	2HD2	56.404	51.623	31.245	20.00
4030	LEU	3HD2	55.893	51.869	29.585	20.00
4031	LEU	N	60.504	52.731	32.420	14.10
4032	LEU	CA	61.690	51.872	32.395	13.57
4033	LEU	C	61.761	50.752	33.479	11.98
4034	LEU	O	62.002	49.612	33.082	10.15
4035	LEU	CB	62.918	52.796	32.471	15.92
4036	LEU	CG	63.686	53.177	31.132	18.96
4037	LEU	CD1	64.024	54.658	31.092	18.76
4038	LEU	CD2	63.078	52.694	29.832	20.15
4039	LEU	H	60.599	53.726	32.457	20.00
4040	LEU	HA	61.655	51.323	31.457	20.00
4041	LEU	1HB	63.669	52.330	33.103	20.00
4042	LEU	2HB	62.658	53.693	33.033	20.00
4043	LEU	HG	64.658	52.680	31.172	20.00
4044	LEU	1HD1	64.621	54.977	31.950	20.00
4045	LEU	2HD1	63.112	55.255	31.098	20.00
4046	LEU	3HD1	64.604	54.927	30.204	20.00

4047	LEU	1HD2	62.022	52.950	29.855	20.00
4048	LEU	2HD2	63.159	51.613	29.727	20.00
4049	LEU	3HD2	63.545	53.169	28.966	20.00
4050	ASP	N	61.560	51.032	34.837	13.06
4051	ASP	CA	61.390	49.905	35.801	12.70
4052	ASP	C	60.231	48.923	35.403	11.44
4053	ASP	O	60.321	47.695	35.475	11.16
4054	ASP	CB	61.278	50.344	37.304	15.05
4055	ASP	CG	62.123	49.288	38.082	23.08
4056	ASP	OD1	63.364	49.262	38.000	22.88
4057	ASP	OD2	61.586	48.379	38.689	24.92
4058	ASP	H	61.491	51.996	35.102	20.00
4059	ASP	HA	62.301	49.314	35.656	20.00
4060	ASP	1HB	60.255	50.372	37.670	20.00
4061	ASP	2HB	61.732	51.315	37.466	20.00
4062	MET	N	59.093	49.516	34.944	13.08
4063	MET	CA	58.001	48.656	34.411	12.59
4064	MET	C	58.462	47.656	33.363	10.76
4065	MET	O	58.113	46.455	33.408	9.86
4066	MET	CB	56.904	49.483	33.836	14.18
4067	MET	CG	55.903	49.698	34.916	20.95
4068	MET	SD	54.280	50.357	34.340	25.25
4069	MET	CE	54.062	51.043	35.991	24.15
4070	MET	H	59.129	50.515	34.915	20.00
4071	MET	HA	57.666	48.053	35.256	20.00
4072	MET	1HB	56.398	49.008	33.008	20.00
4073	MET	2HB	57.229	50.450	33.479	20.00
4074	MET	1HG	56.386	50.456	35.537	20.00
4075	MET	2HG	55.734	48.842	35.576	20.00
4076	MET	1HE	54.838	51.743	36.278	20.00
4077	MET	2HE	54.045	50.220	36.708	20.00
4078	MET	3HE	53.126	51.565	35.960	20.00
4079	ARG	N	59.282	48.214	32.437	11.81
4080	ARG	CA	59.642	47.419	31.226	14.09
4081	ARG	C	60.637	46.252	31.489	14.19
4082	ARG	O	60.925	45.526	30.551	15.37
4083	ARG	CB	59.943	48.311	29.993	15.27
4084	ARG	CG	59.098	49.556	29.941	20.41
4085	ARG	CD	58.376	49.966	28.632	22.57
4086	ARG	NE	59.200	50.017	27.449	21.00
4087	ARG	CZ	58.839	50.296	26.192	19.36
4088	ARG	NH1	57.852	51.031	25.801	17.30
4089	ARG	NH2	59.579	49.731	25.327	15.47
4090	ARG	H	59.531	49.173	32.573	20.00
4091	ARG	HA	58.706	46.936	30.961	20.00
4092	ARG	1HB	59.788	47.723	29.092	20.00
4093	ARG	2HB	60.999	48.599	29.991	20.00
4094	ARG	1HG	59.729	50.392	30.254	20.00
4095	ARG	2HG	58.294	49.528	30.682	20.00
4096	ARG	1HD	57.908	50.943	28.745	20.00
4097	ARG	2HD	57.606	49.239	28.396	20.00
4098	ARG	HE	60.107	49.639	27.637	20.00

4099	ARG	1HH1	57.601	51.294	24.882	20.00
4100	ARG	2HH1	57.261	51.372	26.542	20.00
4101	ARG	1HH2	59.524	49.940	24.352	20.00
4102	ARG	2HH2	60.246	49.058	25.646	20.00
4103	LYS	N	61.164	46.114	32.773	12.82
4104	LYS	CA	61.935	44.941	33.256	11.88
4105	LYS	C	61.085	43.713	33.410	11.52
4106	LYS	O	61.593	42.577	33.421	12.87
4107	LYS	CB	62.641	45.126	34.625	10.90
4108	LYS	CG	63.618	46.277	34.601	10.61
4109	LYS	CD	64.058	46.712	35.985	16.89
4110	LYS	CE	65.109	47.798	35.884	18.25
4111	LYS	NZ	65.603	48.012	37.220	18.64
4112	LYS	H	60.974	46.858	33.419	20.00
4113	LYS	HA	62.681	44.732	32.484	20.00
4114	LYS	1HB	63.115	44.215	34.984	20.00
4115	LYS	2HB	61.880	45.373	35.364	20.00
4116	LYS	1HG	63.158	47.138	34.122	20.00
4117	LYS	2HG	64.500	45.961	34.042	20.00
4118	LYS	1HD	64.460	45.868	36.534	20.00
4119	LYS	2HD	63.195	47.069	36.549	20.00
4120	LYS	1HE	64.731	48.741	35.473	20.00
4121	LYS	2HE	65.940	47.473	35.260	20.00
4122	LYS	1HZ	65.673	47.094	37.707	20.00
4123	LYS	2HZ	64.909	48.549	37.785	20.00
4124	LYS	3HZ	66.557	48.423	37.253	20.00
4125	PHE	N	59.784	43.979	33.518	11.46
4126	PHE	CA	58.890	42.872	33.793	10.66
4127	PHE	C	58.071	42.350	32.647	10.63
4128	PHE	O	57.810	41.174	32.624	11.08
4129	PHE	CB	57.941	43.342	34.873	10.87
4130	PHE	CG	58.702	43.716	36.137	10.74
4131	PHE	CD1	59.198	42.740	36.931	14.67
4132	PHE	CD2	58.946	45.007	36.493	13.16
4133	PHE	CE1	59.928	43.056	38.070	14.61
4134	PHE	CE2	59.709	45.342	37.584	11.84
4135	PHE	CZ	60.231	44.342	38.364	12.78
4136	PHE	H	59.498	44.933	33.611	20.00
4137	PHE	HA	59.449	41.996	34.159	20.00
4138	PHE	1HB	57.244	42.532	35.092	20.00
4139	PHE	2HB	57.356	44.185	34.502	20.00
4140	PHE	HD1	59.026	41.700	36.674	20.00
4141	PHE	HD2	58.541	45.812	35.888	20.00
4142	PHE	HE1	60.292	42.264	38.718	20.00
4143	PHE	HE2	59.892	46.384	37.839	20.00
4144	PHE	HZ	60.833	44.580	39.223	20.00
4145	ARG	N	57.637	43.234	31.729	11.78
4146	ARG	CA	56.999	42.971	30.403	11.12
4147	ARG	C	57.537	43.989	29.272	10.70
4148	ARG	O	57.754	45.168	29.450	11.00
4149	ARG	CB	55.450	43.030	30.422	9.05
4150	ARG	CG	54.720	42.312	29.233	8.54

4151	ARG	CD	53.173	42.198	29.472	8.35
4152	ARG	NE	52.329	41.703	28.413	8.45
4153	ARG	CZ	52.240	40.450	27.919	8.44
4154	ARG	NH1	52.939	39.527	28.425	8.74
4155	ARG	NH2	51.413	40.156	26.940	9.54
4156	ARG	H	57.860	44.166	32.007	20.00
4157	ARG	HA	57.284	41.962	30.171	20.00
4158	ARG	1HB	55.116	44.056	30.542	20.00
4159	ARG	2HB	55.154	42.528	31.341	20.00
4160	ARG	1HG	55.200	41.356	29.029	20.00
4161	ARG	2HG	54.899	42.903	28.332	20.00
4162	ARG	1HD	52.863	43.247	29.522	20.00
4163	ARG	2HD	52.834	41.843	30.446	20.00
4164	ARG	HE	51.722	42.406	28.035	20.00
4165	ARG	1HH1	52.806	38.586	28.112	20.00
4166	ARG	2HH1	53.602	39.812	29.109	20.00
4167	ARG	1HH2	51.312	39.214	26.626	20.00
4168	ARG	2HH2	50.878	40.883	26.495	20.00
4169	MET	N	57.716	43.404	28.075	11.10
4170	MET	CA	58.186	44.260	26.962	10.52
4171	MET	C	57.024	45.223	26.500	12.21
4172	MET	O	55.843	44.858	26.471	11.69
4173	MET	CB	58.606	43.362	25.796	12.40
4174	MET	CG	57.434	42.486	25.214	13.12
4175	MET	SD	57.895	41.619	23.717	12.49
4176	MET	CE	59.286	40.641	24.231	14.52
4177	MET	H	57.157	42.590	27.946	20.00
4178	MET	HA	59.033	44.839	27.332	20.00
4179	MET	1HB	59.421	42.716	26.125	20.00
4180	MET	2HB	59.017	43.981	24.995	20.00
4181	MET	1HG	56.537	43.061	24.993	20.00
4182	MET	2HG	57.153	41.751	25.963	20.00
4183	MET	1HE	58.999	40.071	25.111	20.00
4184	MET	2HE	60.128	41.283	24.473	20.00
4185	MET	3HE	59.569	39.950	23.436	20.00
4186	GLY	N	57.448	46.438	26.060	11.82
4187	GLY	CA	56.696	47.240	25.071	10.69
4188	GLY	C	55.505	47.941	25.724	11.80
4189	GLY	O	54.605	48.408	25.044	11.81
4190	GLY	H	58.395	46.587	26.326	20.00
4191	GLY	1HA	56.379	46.563	24.277	20.00
4192	GLY	2HA	57.369	47.983	24.659	20.00
4193	LEU	N	55.644	48.052	27.083	11.43
4194	LEU	CA	54.762	48.854	27.881	11.39
4195	LEU	C	54.798	50.309	27.386	12.20
4196	LEU	O	55.819	51.000	27.369	12.24
4197	LEU	CB	55.125	48.664	29.353	10.83
4198	LEU	CG	55.153	47.177	29.826	9.47
4199	LEU	CD1	53.979	46.390	29.211	9.16
4200	LEU	CD2	55.106	46.987	31.376	10.38
4201	LEU	H	56.255	47.429	27.563	20.00
4202	LEU	HA	53.765	48.452	27.684	20.00

4203	LEU	1HB	54.363	49.187	29.928	20.00
4204	LEU	2HB	56.038	49.177	29.650	20.00
4205	LEU	HG	56.074	46.731	29.458	20.00
4206	LEU	1HD1	54.146	46.270	28.145	20.00
4207	LEU	2HD1	53.059	46.958	29.330	20.00
4208	LEU	3HD1	53.845	45.402	29.632	20.00
4209	LEU	1HD2	54.239	47.489	31.812	20.00
4210	LEU	2HD2	56.013	47.373	31.822	20.00
4211	LEU	3HD2	55.039	45.931	31.632	20.00
4212	ILE	N	53.611	50.747	26.925	10.54
4213	ILE	CA	53.352	51.904	26.078	11.17
4214	ILE	C	53.942	51.707	24.614	13.75
4215	ILE	O	55.152	51.525	24.341	13.91
4216	ILE	CB	53.775	53.199	26.797	11.11
4217	ILE	CG1	53.323	53.232	28.236	9.13
4218	ILE	CG2	53.534	54.509	25.973	14.38
4219	ILE	CD1	53.085	54.633	28.731	8.65
4220	ILE	H	52.857	50.110	27.076	20.00
4221	ILE	HA	52.300	51.849	25.895	20.00
4222	ILE	HB	54.854	53.154	26.854	20.00
4223	ILE	1HG1	54.057	52.753	28.875	20.00
4224	ILE	2HG1	52.434	52.641	28.395	20.00
4225	ILE	1HG2	52.489	54.771	26.013	20.00
4226	ILE	2HG2	53.837	54.423	24.931	20.00
4227	ILE	3HG2	54.073	55.352	26.405	20.00
4228	ILE	1HD1	52.339	55.011	28.055	20.00
4229	ILE	2HD1	53.956	55.277	28.718	20.00
4230	ILE	3HD1	52.642	54.642	29.720	20.00
4231	GLN	N	52.962	51.794	23.698	13.18
4232	GLN	CA	53.199	51.506	22.275	12.31
4233	GLN	C	53.430	52.716	21.367	14.51
4234	GLN	O	53.955	52.560	20.262	14.93
4235	GLN	CB	52.144	50.560	21.736	12.10
4236	GLN	CG	52.439	49.160	22.274	13.08
4237	GLN	CD	53.546	48.547	21.425	14.33
4238	GLN	OE1	53.483	48.340	20.241	16.45
4239	GLN	NE2	54.621	48.324	22.095	11.97
4240	GLN	H	52.069	52.116	24.025	20.00
4241	GLN	HA	54.053	50.882	22.198	20.00
4242	GLN	1HB	52.148	50.567	20.649	20.00
4243	GLN	2HB	51.163	50.906	22.068	20.00
4244	GLN	1HG	51.565	48.532	22.129	20.00
4245	GLN	2HG	52.700	49.128	23.334	20.00
4246	GLN	1HE2	55.255	47.877	21.463	20.00
4247	GLN	2HE2	54.687	48.534	23.072	20.00
4248	THR	N	52.999	53.889	21.847	14.47
4249	THR	CA	53.293	55.112	21.160	13.82
4250	THR	C	53.795	56.277	22.022	15.31
4251	THR	O	53.504	56.378	23.202	15.21
4252	THR	CB	52.018	55.721	20.549	12.44
4253	THR	OG1	51.132	56.387	21.467	13.84
4254	THR	CG2	51.116	54.688	19.900	12.80

4255	THR	H	52.517	53.881	22.722	20.00
4256	THR	HA	54.032	54.925	20.382	20.00
4257	THR	HB	52.313	56.216	19.551	20.00
4258	THR	HG1	51.470	57.060	22.111	20.00
4259	THR	1HG2	50.910	53.814	20.510	20.00
4260	THR	2HG2	51.562	54.409	18.964	20.00
4261	THR	3HG2	50.153	55.136	19.640	20.00
4262	ALA	N	54.477	57.213	21.304	16.12
4263	ALA	CA	54.775	58.515	21.914	17.15
4264	ALA	C	53.591	59.401	22.373	17.06
4265	ALA	O	53.789	60.142	23.290	16.84
4266	ALA	CB	55.595	59.324	20.904	15.40
4267	ALA	H	54.845	56.937	20.420	20.00
4268	ALA	HA	55.376	58.310	22.799	20.00
4269	ALA	1HB	55.020	59.526	19.991	20.00
4270	ALA	2HB	56.466	58.733	20.623	20.00
4271	ALA	3HB	55.932	60.276	21.309	20.00
4272	ASP	N	52.372	59.361	21.793	16.67
4273	ASP	CA	51.253	60.117	22.425	16.05
4274	ASP	C	50.459	59.397	23.628	14.16
4275	ASP	O	49.950	60.007	24.564	13.25
4276	ASP	CB	50.285	60.449	21.279	16.36
4277	ASP	CG	49.302	61.573	21.733	18.91
4278	ASP	OD1	49.622	62.439	22.570	19.27
4279	ASP	OD2	48.176	61.536	21.255	19.47
4280	ASP	H	52.169	58.892	20.940	20.00
4281	ASP	HA	51.675	61.041	22.821	20.00
4282	ASP	1HB	49.700	59.570	21.004	20.00
4283	ASP	2HB	50.796	60.835	20.398	20.00
4284	GLN	N	50.509	58.059	23.612	12.74
4285	GLN	CA	50.357	57.350	24.885	12.47
4286	GLN	C	51.372	57.732	25.883	13.42
4287	GLN	O	50.983	57.853	27.011	13.68
4288	GLN	CB	50.268	55.796	24.870	10.94
4289	GLN	CG	49.003	55.278	24.131	10.93
4290	GLN	CD	49.169	53.862	23.674	11.89
4291	GLN	OE1	50.245	53.338	23.823	13.27
4292	GLN	NE2	48.120	53.148	23.278	10.17
4293	GLN	H	50.220	57.686	22.728	20.00
4294	GLN	HA	49.410	57.687	25.306	20.00
4295	GLN	1HB	50.120	55.691	25.933	20.00
4296	GLN	2HB	51.199	55.298	24.622	20.00
4297	GLN	1HG	48.722	55.880	23.275	20.00
4298	GLN	2HG	48.157	55.324	24.814	20.00
4299	GLN	1HE2	48.192	52.170	23.170	20.00
4300	GLN	2HE2	47.274	53.670	23.184	20.00
4301	LEU	N	52.632	57.962	25.482	15.21
4302	LEU	CA	53.622	58.317	26.460	13.64
4303	LEU	C	53.221	59.639	27.103	14.41
4304	LEU	O	53.197	59.793	28.299	15.65
4305	LEU	CB	55.040	58.373	25.963	12.86
4306	LEU	CG	55.940	58.940	27.044	13.02

4307	LEU	CD1	57.423	59.114	26.568	12.87
4308	LEU	CD2	55.803	58.093	28.344	12.32
4309	LEU	H	52.853	57.713	24.542	20.00
4310	LEU	HA	53.697	57.475	27.137	20.00
4311	LEU	1HB	55.109	58.990	25.075	20.00
4312	LEU	2HB	55.368	57.378	25.665	20.00
4313	LEU	HG	55.643	59.956	27.299	20.00
4314	LEU	1HD1	57.503	59.794	25.718	20.00
4315	LEU	2HD1	57.826	58.155	26.246	20.00
4316	LEU	3HD1	58.066	59.498	27.365	20.00
4317	LEU	1HD2	55.984	57.030	28.190	20.00
4318	LEU	2HD2	54.823	58.181	28.813	20.00
4319	LEU	3HD2	56.521	58.432	29.090	20.00
4320	ARG	N	52.940	60.581	26.220	13.43
4321	ARG	CA	52.516	61.919	26.552	13.38
4322	ARG	C	51.245	61.967	27.425	14.16
4323	ARG	O	51.086	62.719	28.402	14.64
4324	ARG	CB	52.251	62.603	25.232	13.46
4325	ARG	CG	51.762	64.060	25.435	13.29
4326	ARG	CD	51.576	64.868	24.119	16.52
4327	ARG	NE	51.522	66.299	24.432	20.17
4328	ARG	CZ	50.397	67.002	24.409	19.49
4329	ARG	NH1	49.216	66.446	24.187	20.88
4330	ARG	NH2	50.463	68.265	24.567	21.32
4331	ARG	H	53.137	60.365	25.265	20.00
4332	ARG	HA	53.333	62.403	27.095	20.00
4333	ARG	1HB	51.506	62.063	24.656	20.00
4334	ARG	2HB	53.170	62.609	24.642	20.00
4335	ARG	1HG	52.524	64.576	26.019	20.00
4336	ARG	2HG	50.846	64.108	26.022	20.00
4337	ARG	1HD	50.719	64.529	23.542	20.00
4338	ARG	2HD	52.437	64.758	23.467	20.00
4339	ARG	HE	52.358	66.829	24.622	20.00
4340	ARG	1HH1	48.378	66.959	24.120	20.00
4341	ARG	2HH1	49.238	65.453	24.060	20.00
4342	ARG	1HH2	49.696	68.881	24.571	20.00
4343	ARG	2HH2	51.389	68.673	24.644	20.00
4344	PHE	N	50.335	61.083	26.968	13.41
4345	PHE	CA	49.001	61.017	27.582	13.00
4346	PHE	C	49.112	60.777	29.110	12.42
4347	PHE	O	48.608	61.592	29.880	14.84
4348	PHE	CB	48.098	60.098	26.822	12.87
4349	PHE	CG	46.828	60.022	27.581	13.08
4350	PHE	CD1	45.801	60.881	27.276	15.82
4351	PHE	CD2	46.705	59.168	28.680	13.48
4352	PHE	CE1	44.667	60.910	28.097	14.88
4353	PHE	CE2	45.574	59.191	29.498	14.71
4354	PHE	CZ	44.540	60.071	29.199	13.48
4355	PHE	H	50.562	60.635	26.109	20.00
4356	PHE	HA	48.585	62.029	27.497	20.00
4357	PHE	1HB	48.536	59.108	26.759	20.00
4358	PHE	2HB	47.915	60.462	25.813	20.00

4359	PHE	HD1	45.882	61.539	26.423	20.00
4360	PHE	HD2	47.512	58.491	28.940	20.00
4361	PHE	HE1	43.859	61.581	27.846	20.00
4362	PHE	HE2	45.506	58.535	30.360	20.00
4363	PHE	HZ	43.642	60.078	29.799	20.00
4364	SER	N	49.969	59.763	29.464	12.86
4365	SER	CA	50.587	59.542	30.810	13.82
4366	SER	C	51.041	60.698	31.656	15.06
4367	SER	O	50.771	60.701	32.874	15.36
4368	SER	CB	51.858	58.721	30.716	11.50
4369	SER	OG	51.516	57.632	29.848	19.07
4370	SER	H	50.242	59.181	28.697	20.00
4371	SER	HA	49.818	59.037	31.402	20.00
4372	SER	1HB	52.010	58.296	31.729	20.00
4373	SER	2HB	52.852	59.284	30.654	20.00
4374	SER	HG	51.270	57.729	28.858	20.00
4375	TYR	N	51.813	61.593	31.024	14.37
4376	TYR	CA	52.267	62.766	31.766	13.98
4377	TYR	C	51.058	63.681	31.998	14.72
4378	TYR	O	50.967	64.337	33.005	16.92
4379	TYR	CB	53.229	63.600	30.917	15.56
4380	TYR	CG	54.652	63.274	30.954	15.10
4381	TYR	CD1	55.052	62.134	30.271	15.01
4382	TYR	CD2	55.620	64.132	31.549	16.69
4383	TYR	CE1	56.421	61.838	30.141	17.26
4384	TYR	CE2	57.005	63.819	31.493	17.79
4385	TYR	CZ	57.399	62.668	30.725	18.91
4386	TYR	OH	58.714	62.271	30.439	22.03
4387	TYR	H	51.999	61.445	30.050	20.00
4388	TYR	HA	52.676	62.473	32.734	20.00
4389	TYR	1HB	53.169	64.651	31.202	20.00
4390	TYR	2HB	52.902	63.592	29.873	20.00
4391	TYR	HD1	54.327	61.491	29.785	20.00
4392	TYR	HD2	55.300	65.033	32.057	20.00
4393	TYR	HE1	56.711	60.965	29.563	20.00
4394	TYR	HE2	57.650	64.487	32.074	20.00
4395	TYR	HH	59.145	62.947	29.940	20.00
4396	LEU	N	50.119	63.730	31.072	14.60
4397	LEU	CA	48.847	64.446	31.233	13.80
4398	LEU	C	47.979	63.736	32.311	13.84
4399	LEU	O	47.376	64.413	33.100	15.22
4400	LEU	CB	48.123	64.423	29.847	15.22
4401	LEU	CG	47.836	65.699	28.996	17.91
4402	LEU	CD1	47.984	65.297	27.542	17.36
4403	LEU	CD2	48.732	66.869	29.241	17.38
4404	LEU	H	50.299	63.237	30.217	20.00
4405	LEU	HA	49.052	65.467	31.565	20.00
4406	LEU	1HB	47.178	63.886	29.921	20.00
4407	LEU	2HB	48.719	63.775	29.209	20.00
4408	LEU	HG	46.811	66.008	29.196	20.00
4409	LEU	1HD1	47.280	64.485	27.341	20.00
4410	LEU	2HD1	48.978	64.923	27.304	20.00

4411	LEU	3HD1	47.734	66.112	26.869	20.00
4412	LEU	1HD2	49.761	66.547	29.286	20.00
4413	LEU	2HD2	48.501	67.327	30.203	20.00
4414	LEU	3HD2	48.593	67.645	28.487	20.00
4415	ALA	N	47.923	62.376	32.381	13.18
4416	ALA	CA	47.070	61.732	33.394	12.65
4417	ALA	C	47.647	61.860	34.804	14.16
4418	ALA	O	46.924	62.169	35.735	14.00
4419	ALA	CB	46.896	60.294	33.069	13.02
4420	ALA	H	48.404	61.889	31.656	20.00
4421	ALA	HA	46.109	62.245	33.400	20.00
4422	ALA	1HB	47.848	59.772	33.044	20.00
4423	ALA	2HB	46.427	60.175	32.093	20.00
4424	ALA	3HB	46.257	59.808	33.797	20.00
4425	VAL	N	48.993	61.669	34.953	11.78
4426	VAL	CA	49.638	61.928	36.266	12.53
4427	VAL	C	49.529	63.388	36.657	13.82
4428	VAL	O	49.106	63.654	37.760	12.86
4429	VAL	CB	51.060	61.470	36.199	11.66
4430	VAL	CG1	51.011	59.975	35.935	13.24
4431	VAL	CG2	51.884	61.820	37.450	9.92
4432	VAL	H	49.505	61.389	34.142	20.00
4433	VAL	HA	49.097	61.346	37.011	20.00
4434	VAL	HB	51.525	61.950	35.339	20.00
4435	VAL	1HG1	50.457	59.680	35.046	20.00
4436	VAL	2HG1	50.567	59.443	36.774	20.00
4437	VAL	3HG1	52.028	59.609	35.790	20.00
4438	VAL	1HG2	51.434	61.452	38.374	20.00
4439	VAL	2HG2	52.023	62.899	37.543	20.00
4440	VAL	3HG2	52.878	61.383	37.357	20.00
4441	ILE	N	49.859	64.316	35.726	12.29
4442	ILE	CA	49.777	65.753	36.099	13.94
4443	ILE	C	48.339	66.176	36.660	14.15
4444	ILE	O	48.117	66.660	37.773	14.06
4445	ILE	CB	50.394	66.654	34.959	13.50
4446	ILE	CG1	51.944	66.544	34.796	14.91
4447	ILE	CG2	50.076	68.142	35.160	12.74
4448	ILE	CD1	52.435	66.779	33.323	13.99
4449	ILE	H	50.221	64.029	34.834	20.00
4450	ILE	HA	50.451	65.871	36.951	20.00
4451	ILE	HB	49.927	66.358	34.020	20.00
4452	ILE	1HG1	52.222	65.531	35.081	20.00
4453	ILE	2HG1	52.448	67.206	35.500	20.00
4454	ILE	1HG2	50.457	68.501	36.112	20.00
4455	ILE	2HG2	49.002	68.322	35.154	20.00
4456	ILE	3HG2	50.501	68.767	34.372	20.00
4457	ILE	1HD1	52.530	67.849	33.137	20.00
4458	ILE	2HD1	51.774	66.409	32.552	20.00
4459	ILE	3HD1	53.420	66.336	33.174	20.00
4460	GLU	N	47.359	65.839	35.881	13.27
4461	GLU	CA	45.989	66.067	36.314	12.79
4462	GLU	C	45.607	65.346	37.640	14.22

4463	GLU	O	45.016	65.931	38.541	14.98
4464	GLU	CB	45.069	65.673	35.120	11.88
4465	GLU	CG	43.617	66.022	35.440	12.69
4466	GLU	CD	43.489	67.515	35.873	18.61
4467	GLU	OE1	44.197	68.391	35.267	19.68
4468	GLU	OE2	42.684	67.786	36.795	20.07
4469	GLU	H	47.536	65.473	34.961	20.00
4470	GLU	HA	45.923	67.146	36.510	20.00
4471	GLU	1HB	45.179	64.633	34.870	20.00
4472	GLU	2HB	45.379	66.212	34.239	20.00
4473	GLU	1HG	43.215	65.380	36.227	20.00
4474	GLU	2HG	42.978	65.886	34.565	20.00
4475	GLY	N	46.045	64.072	37.760	14.10
4476	GLY	CA	45.654	63.221	38.876	11.35
4477	GLY	C	46.321	63.593	40.191	12.42
4478	GLY	O	45.815	63.292	41.292	14.09
4479	GLY	H	46.512	63.723	36.945	20.00
4480	GLY	1HA	45.949	62.203	38.620	20.00
4481	GLY	2HA	44.571	63.247	38.973	20.00
4482	ALA	N	47.519	64.244	40.018	12.11
4483	ALA	CA	48.374	64.823	41.082	13.24
4484	ALA	C	47.582	65.702	41.977	14.50
4485	ALA	O	47.596	65.589	43.194	15.74
4486	ALA	CB	49.490	65.703	40.494	12.85
4487	ALA	H	47.815	64.323	39.062	20.00
4488	ALA	HA	48.781	63.986	41.661	20.00
4489	ALA	1HB	49.117	66.579	39.973	20.00
4490	ALA	2HB	50.058	65.139	39.757	20.00
4491	ALA	3HB	50.202	66.027	41.246	20.00
4492	LYS	N	46.816	66.546	41.296	15.43
4493	LYS	CA	45.724	67.345	41.899	17.97
4494	LYS	C	44.931	66.779	43.125	18.17
4495	LYS	O	44.899	67.351	44.214	16.72
4496	LYS	CB	44.741	67.668	40.789	17.36
4497	LYS	CG	45.473	68.507	39.735	20.89
4498	LYS	CD	44.411	69.357	39.059	19.35
4499	LYS	CE	44.941	70.273	37.899	21.45
4500	LYS	NZ	43.854	70.561	36.916	28.58
4501	LYS	H	46.970	66.537	40.302	20.00
4502	LYS	HA	46.194	68.257	42.271	20.00
4503	LYS	1HB	43.929	68.238	41.230	20.00
4504	LYS	2HB	44.281	66.774	40.403	20.00
4505	LYS	1HG	46.030	67.909	39.021	20.00
4506	LYS	2HG	46.191	69.182	40.190	20.00
4507	LYS	1HD	43.864	69.945	39.793	20.00
4508	LYS	2HD	43.678	68.654	38.678	20.00
4509	LYS	1HE	45.750	69.766	37.367	20.00
4510	LYS	2HE	45.330	71.199	38.323	20.00
4511	LYS	1HZ	42.957	70.859	37.339	20.00
4512	LYS	2HZ	43.637	69.601	36.519	20.00
4513	LYS	3HZ	44.134	71.121	36.095	20.00
4514	PHE	N	44.281	65.638	42.830	17.06

4515	PHE	CA	43.646	64.836	43.843	17.26
4516	PHE	C	44.714	64.518	44.920	17.65
4517	PHE	O	44.482	64.738	46.105	17.35
4518	PHE	CB	42.997	63.581	43.127	16.04
4519	PHE	CG	42.385	62.573	44.092	18.17
4520	PHE	CD1	43.226	61.617	44.720	18.77
4521	PHE	CD2	41.030	62.660	44.476	17.46
4522	PHE	CE1	42.767	60.863	45.818	18.56
4523	PHE	CE2	40.577	61.903	45.587	17.26
4524	PHE	CZ	41.444	61.051	46.279	16.76
4525	PHE	H	44.444	65.270	41.908	20.00
4526	PHE	HA	42.892	65.451	44.341	20.00
4527	PHE	1HB	43.750	63.045	42.548	20.00
4528	PHE	2HB	42.235	63.919	42.431	20.00
4529	PHE	HD1	44.244	61.511	44.366	20.00
4530	PHE	HD2	40.363	63.332	43.956	20.00
4531	PHE	HE1	43.447	60.182	46.317	20.00
4532	PHE	HE2	39.540	61.973	45.889	20.00
4533	PHE	HZ	41.096	60.520	47.152	20.00
4534	ILE	N	45.904	64.058	44.464	17.16
4535	ILE	CA	46.963	63.619	45.424	16.95
4536	ILE	C	47.403	64.740	46.364	18.22
4537	ILE	O	47.734	64.521	47.537	19.58
4538	ILE	CB	48.233	63.056	44.686	16.65
4539	ILE	CG1	47.877	61.897	43.715	15.20
4540	ILE	CG2	49.381	62.644	45.664	17.33
4541	ILE	CD1	47.124	60.747	44.386	16.00
4542	ILE	H	46.085	64.029	43.475	20.00
4543	ILE	HA	46.533	62.830	46.038	20.00
4544	ILE	HB	48.696	63.820	44.061	20.00
4545	ILE	1HG1	48.782	61.500	43.247	20.00
4546	ILE	2HG1	47.269	62.310	42.913	20.00
4547	ILE	1HG2	49.052	61.908	46.381	20.00
4548	ILE	2HG2	49.782	63.508	46.200	20.00
4549	ILE	3HG2	50.229	62.212	45.127	20.00
4550	ILE	1HD1	46.267	61.066	44.967	20.00
4551	ILE	2HD1	47.811	60.254	45.053	20.00
4552	ILE	3HD1	46.779	60.010	43.663	20.00
4553	MET	N	47.484	65.937	45.795	17.76
4554	MET	CA	48.123	67.010	46.548	17.15
4555	MET	C	47.180	67.601	47.549	18.59
4556	MET	O	47.634	68.088	48.582	18.92
4557	MET	CB	48.913	67.951	45.663	18.33
4558	MET	CG	50.089	67.168	45.027	18.10
4559	MET	SD	51.391	66.428	46.158	22.98
4560	MET	CE	51.905	67.914	47.025	22.14
4561	MET	H	47.175	66.080	44.861	20.00
4562	MET	HA	48.874	66.553	47.202	20.00
4563	MET	1HB	49.285	68.791	46.230	20.00
4564	MET	2HB	48.257	68.389	44.906	20.00
4565	MET	1HG	50.607	67.834	44.333	20.00
4566	MET	2HG	49.687	66.363	44.396	20.00

4567	MET	1HE	51.085	68.420	47.548	20.00
4568	MET	2HE	52.319	68.603	46.291	20.00
4569	MET	3HE	52.687	67.673	47.749	20.00
4570	GLY	N	45.872	67.378	47.277	17.81
4571	GLY	CA	44.850	67.320	48.361	19.24
4572	GLY	C	43.474	67.982	48.080	18.12
4573	GLY	O	42.634	68.149	48.984	18.31
4574	GLY	H	45.672	66.962	46.387	20.00
4575	GLY	1HA	45.269	67.841	49.231	20.00
4576	GLY	2HA	44.716	66.282	48.674	20.00
4577	ASP	N	43.290	68.369	46.814	16.53
4578	ASP	CA	41.961	68.826	46.372	17.00
4579	ASP	C	41.035	67.607	46.048	18.13
4580	ASP	O	40.855	67.207	44.903	19.06
4581	ASP	CB	42.133	69.714	45.111	18.82
4582	ASP	CG	40.838	69.926	44.250	20.22
4583	ASP	OD1	39.720	69.692	44.750	19.51
4584	ASP	OD2	40.968	70.317	43.089	23.56
4585	ASP	H	44.012	68.210	46.144	20.00
4586	ASP	HA	41.478	69.396	47.157	20.00
4587	ASP	1HB	42.844	69.226	44.444	20.00
4588	ASP	2HB	42.546	70.691	45.349	20.00
4589	SER	N	40.427	66.964	47.031	18.73
4590	SER	CA	39.684	65.767	46.555	16.96
4591	SER	C	38.438	66.178	45.684	18.39
4592	SER	O	37.753	65.300	45.151	18.33
4593	SER	CB	39.548	64.762	47.784	17.13
4594	SER	OG	40.769	64.296	48.566	14.25
4595	SER	H	40.606	67.273	47.975	20.00
4596	SER	HA	40.219	65.218	45.768	20.00
4597	SER	1HB	38.927	63.897	47.443	20.00
4598	SER	2HB	38.817	65.230	48.491	20.00
4599	SER	HG	41.719	64.490	48.317	20.00
4600	SER	N	38.161	67.528	45.516	17.50
4601	SER	CA	37.016	68.024	44.673	18.74
4602	SER	C	37.183	67.715	43.164	17.75
4603	SER	O	36.183	67.406	42.477	16.68
4604	SER	CB	36.747	69.546	44.774	19.67
4605	SER	OG	37.500	70.494	43.897	21.88
4606	SER	H	38.797	68.224	45.866	20.00
4607	SER	HA	36.131	67.483	45.019	20.00
4608	SER	1HB	36.605	69.852	45.852	20.00
4609	SER	2HB	35.674	69.626	44.497	20.00
4610	SER	HG	38.484	70.378	43.663	20.00
4611	VAL	N	38.473	67.708	42.702	17.27
4612	VAL	CA	38.680	67.191	41.319	18.22
4613	VAL	C	37.910	65.970	40.883	18.73
4614	VAL	O	37.472	65.906	39.737	19.63
4615	VAL	CB	40.132	66.911	40.897	20.69
4616	VAL	CG1	40.884	66.073	41.910	17.79
4617	VAL	CG2	40.868	68.222	40.572	23.70
4618	VAL	H	39.207	68.134	43.257	20.00

4619	VAL	HA	38.305	67.980	40.690	20.00
4620	VAL	HB	40.169	66.379	39.947	20.00
4621	VAL	1HG1	40.410	65.103	42.049	20.00
4622	VAL	2HG1	40.897	66.580	42.855	20.00
4623	VAL	3HG1	41.920	65.935	41.604	20.00
4624	VAL	1HG2	41.042	68.758	41.495	20.00
4625	VAL	2HG2	40.304	68.883	39.916	20.00
4626	VAL	3HG2	41.836	68.034	40.111	20.00
4627	GLN	N	37.827	64.997	41.788	18.28
4628	GLN	CA	37.407	63.664	41.383	19.78
4629	GLN	C	35.957	63.564	40.980	23.25
4630	GLN	O	35.635	62.870	40.010	25.12
4631	GLN	CB	37.684	62.612	42.412	20.56
4632	GLN	CG	37.171	61.233	41.947	24.84
4633	GLN	CD	37.628	60.156	42.928	27.26
4634	GLN	OE1	38.497	60.357	43.777	31.04
4635	GLN	NE2	37.005	59.010	42.735	29.42
4636	GLN	H	38.155	65.203	42.714	20.00
4637	GLN	HA	37.983	63.430	40.496	20.00
4638	GLN	1HB	37.199	62.866	43.353	20.00
4639	GLN	2HB	38.752	62.567	42.609	20.00
4640	GLN	1HG	37.541	60.972	40.956	20.00
4641	GLN	2HG	36.077	61.187	41.899	20.00
4642	GLN	1HE2	37.189	58.293	43.411	20.00
4643	GLN	2HE2	36.335	58.854	42.017	20.00
4644	ASP	N	35.132	64.360	41.665	25.31
4645	ASP	CA	33.794	64.542	41.078	27.02
4646	ASP	C	33.714	65.515	39.851	25.79
4647	ASP	O	33.010	65.234	38.884	25.32
4648	ASP	CB	32.728	64.363	42.176	35.78
4649	ASP	CG	32.232	62.848	42.252	44.92
4650	ASP	OD1	33.060	61.924	42.012	50.04
4651	ASP	OD2	31.014	62.626	42.502	50.59
4652	ASP	H	35.428	64.744	42.538	20.00
4653	ASP	HA	33.606	63.669	40.453	20.00
4654	ASP	1HB	31.871	64.981	41.929	20.00
4655	ASP	2HB	33.104	64.706	43.143	20.00
4656	GLN	N	34.626	66.532	39.807	23.38
4657	GLN	CA	34.903	67.171	38.484	24.32
4658	GLN	C	35.209	66.229	37.269	23.16
4659	GLN	O	34.689	66.444	36.165	21.27
4660	GLN	CB	35.989	68.248	38.513	28.00
4661	GLN	CG	35.765	69.233	39.647	35.72
4662	GLN	CD	37.011	70.084	39.806	43.13
4663	GLN	OE1	37.614	70.466	38.814	48.57
4664	GLN	NE2	37.399	70.384	41.059	43.82
4665	GLN	H	35.105	66.754	40.660	20.00
4666	GLN	HA	33.969	67.668	38.222	20.00
4667	GLN	1HB	36.001	68.784	37.562	20.00
4668	GLN	2HB	36.973	67.792	38.594	20.00
4669	GLN	1HG	35.574	68.757	40.601	20.00
4670	GLN	2HG	34.922	69.879	39.419	20.00

4671	GLN	1HE2	38.245	70.918	41.061	20.00
4672	GLN	2HE2	36.969	70.145	41.925	20.00
4673	TRP	N	36.067	65.207	37.463	20.29
4674	TRP	CA	36.319	64.264	36.366	19.31
4675	TRP	C	35.089	63.487	35.918	19.07
4676	TRP	O	34.861	63.193	34.736	19.20
4677	TRP	CB	37.263	63.169	36.885	19.26
4678	TRP	CG	38.589	63.776	37.213	15.65
4679	TRP	CD1	39.188	64.909	36.656	14.94
4680	TRP	CD2	39.483	63.209	38.143	15.85
4681	TRP	NE1	40.412	65.088	37.205	15.54
4682	TRP	CE2	40.619	64.068	38.133	15.86
4683	TRP	CE3	39.390	62.115	38.989	14.86
4684	TRP	CZ2	41.699	63.722	38.904	16.78
4685	TRP	CZ3	40.479	61.761	39.786	14.37
4686	TRP	CH2	41.631	62.585	39.740	15.56
4687	TRP	H	36.508	65.153	38.360	20.00
4688	TRP	HA	36.722	64.799	35.513	20.00
4689	TRP	1HB	37.452	62.427	36.116	20.00
4690	TRP	2HB	36.849	62.663	37.759	20.00
4691	TRP	HD1	38.745	65.543	35.900	20.00
4692	TRP	HE1	41.059	65.811	37.001	20.00
4693	TRP	HE3	38.490	61.508	38.989	20.00
4694	TRP	HZ2	42.571	64.373	38.864	20.00
4695	TRP	HZ3	40.436	60.909	40.460	20.00
4696	TRP	HH2	42.485	62.328	40.349	20.00
4697	LYS	N	34.338	63.136	36.976	21.19
4698	LYS	CA	33.082	62.421	36.730	24.17
4699	LYS	C	32.154	63.264	35.758	25.28
4700	LYS	O	31.736	62.892	34.656	26.15
4701	LYS	CB	32.453	62.137	38.108	26.43
4702	LYS	CG	31.329	61.095	38.057	32.00
4703	LYS	CD	30.909	60.906	39.490	38.87
4704	LYS	CE	29.764	59.913	39.692	45.47
4705	LYS	NZ	29.279	60.040	41.099	51.74
4706	LYS	H	34.648	63.302	37.917	20.00
4707	LYS	HA	33.334	61.452	36.303	20.00
4708	LYS	1HB	32.101	63.055	38.569	20.00
4709	LYS	2HB	33.239	61.739	38.752	20.00
4710	LYS	1HG	31.674	60.151	37.631	20.00
4711	LYS	2HG	30.495	61.432	37.435	20.00
4712	LYS	1HD	30.615	61.873	39.902	20.00
4713	LYS	2HD	31.768	60.576	40.078	20.00
4714	LYS	1HE	30.136	58.898	39.499	20.00
4715	LYS	2HE	28.947	60.090	38.984	20.00
4716	LYS	1HZ	29.033	61.040	41.269	20.00
4717	LYS	2HZ	30.103	59.869	41.719	20.00
4718	LYS	3HZ	28.496	59.397	41.317	20.00
4719	GLU	N	32.050	64.521	36.209	26.22
4720	GLU	CA	31.455	65.533	35.365	27.87
4721	GLU	C	32.006	65.577	33.869	26.53
4722	GLU	O	31.332	65.367	32.866	30.42

4723	GLU	CB	31.542	66.807	36.263	34.80
4724	GLU	CG	30.693	66.725	37.585	47.61
4725	GLU	CD	29.211	66.293	37.462	55.88
4726	GLU	OE1	28.422	67.129	36.998	59.76
4727	GLU	OE2	28.883	65.134	37.826	61.03
4728	GLU	H	32.243	64.712	37.176	20.00
4729	GLU	HA	30.410	65.251	35.271	20.00
4730	GLU	1HB	31.181	67.661	35.698	20.00
4731	GLU	2HB	32.564	67.009	36.547	20.00
4732	GLU	1HG	30.708	67.672	38.117	20.00
4733	GLU	2HG	31.080	65.993	38.276	20.00
4734	LEU	N	33.317	65.813	33.793	24.19
4735	LEU	CA	34.088	66.004	32.540	23.43
4736	LEU	C	34.108	64.773	31.610	24.08
4737	LEU	O	34.441	64.885	30.447	22.85
4738	LEU	CB	35.553	66.277	32.956	25.02
4739	LEU	CG	35.989	67.725	32.878	25.39
4740	LEU	CD1	37.358	67.805	33.605	27.03
4741	LEU	CD2	34.947	68.615	33.583	28.40
4742	LEU	H	33.756	65.871	34.690	20.00
4743	LEU	HA	33.699	66.832	31.949	20.00
4744	LEU	1HB	36.274	65.707	32.372	20.00
4745	LEU	2HB	35.693	65.929	33.976	20.00
4746	LEU	HG	36.089	68.033	31.838	20.00
4747	LEU	1HD1	38.106	67.202	33.097	20.00
4748	LEU	2HD1	37.284	67.450	34.634	20.00
4749	LEU	3HD1	37.742	68.825	33.641	20.00
4750	LEU	1HD2	34.769	68.279	34.605	20.00
4751	LEU	2HD2	33.982	68.644	33.078	20.00
4752	LEU	3HD2	35.307	69.642	33.676	20.00
4753	SER	N	33.842	63.591	32.146	23.22
4754	SER	CA	34.023	62.430	31.279	24.53
4755	SER	C	32.729	62.144	30.475	26.87
4756	SER	O	32.753	61.539	29.414	26.47
4757	SER	CB	34.168	61.268	32.238	23.92
4758	SER	OG	32.851	60.942	32.814	27.33
4759	SER	H	33.548	63.568	33.105	20.00
4760	SER	HA	34.900	62.512	30.638	20.00
4761	SER	1HB	35.074	61.383	32.907	20.00
4762	SER	2HB	34.520	60.416	31.633	20.00
4763	SER	HG	32.219	61.568	33.301	20.00
4764	HIS	N	31.582	62.546	31.085	29.80
4765	HIS	CA	30.257	62.150	30.557	33.13
4766	HIS	C	29.778	60.651	30.861	33.64
4767	HIS	O	29.195	59.996	29.999	31.30
4768	HIS	CB	30.150	62.548	29.063	36.51
4769	HIS	CG	30.638	63.959	28.940	40.71
4770	HIS	ND1	31.746	64.287	28.246	43.97
4771	HIS	CD2	30.108	65.137	29.519	42.68
4772	HIS	CE1	31.894	65.632	28.386	43.60
4773	HIS	NE2	30.917	66.174	29.151	42.67
4774	HIS	H	31.682	63.199	31.841	20.00

4775	HIS	HA	29.569	62.773	31.127	20.00
4776	HIS	1HB	29.124	62.477	28.704	20.00
4777	HIS	2HB	30.767	61.968	28.391	20.00
4778	HIS	HD1	32.351	63.667	27.792	20.00
4779	HIS	HD2	29.244	65.194	30.166	20.00
4780	HIS	HE1	32.696	66.220	27.957	20.00
4781	GLU	N	30.038	60.148	32.122	35.19
4782	GLU	CA	29.812	58.725	32.461	36.70
4783	GLU	C	28.365	58.293	32.195	38.60
4784	GLU	O	28.187	57.171	31.764	37.53
4785	GLU	CB	30.385	58.171	33.820	35.82
4786	GLU	CG	29.685	58.624	35.121	36.20
4787	GLU	CD	30.185	57.959	36.421	38.96
4788	GLU	OE1	31.324	57.527	36.458	36.60
4789	GLU	OE2	29.434	57.837	37.399	41.14
4790	GLU	H	30.309	60.799	32.826	20.00
4791	GLU	HA	30.412	58.167	31.757	20.00
4792	GLU	1HB	31.453	58.377	33.892	20.00
4793	GLU	2HB	30.305	57.095	33.743	20.00
4794	GLU	1HG	28.617	58.448	35.059	20.00
4795	GLU	2HG	29.808	59.700	35.259	20.00
4796	ASP	N	27.355	59.161	32.427	42.63
4797	ASP	CA	25.947	58.715	32.232	46.40
4798	ASP	C	25.333	59.095	30.796	47.19
4799	ASP	O	25.663	60.179	30.242	46.38
4800	ASP	CB	25.156	59.121	33.508	50.98
4801	ASP	CG	25.757	58.386	34.723	57.85
4802	ASP	OD1	25.724	57.146	34.731	60.50
4803	ASP	OD2	26.292	59.021	35.648	61.02
4804	ASP	OXT	24.582	58.276	30.208	48.57
4805	ASP	H	27.519	60.002	32.926	20.00
4806	ASP	HA	25.950	57.622	32.219	20.00
4807	ASP	1HB	24.118	58.815	33.431	20.00
4808	ASP	2HB	25.188	60.198	33.649	20.00
1	OC_	C1	49.640	37.719	14.003	0.00
2	OC_	C2	50.787	38.141	14.736	0.00
3	OC_	C3	51.008	39.495	14.916	0.00
4	OC_	C4	50.154	40.364	14.322	0.00
5	OC_	C5	49.053	40.047	13.581	0.00
6	OC_	C6	48.782	38.701	13.402	0.00
7	OC_	7H	49.187	36.718	13.842	0.00
8	OC_	8H	48.426	40.820	13.123	0.00
9	OC_	H9	47.921	38.415	12.808	0.00
10	OC_	C10	52.036	40.299	15.636	0.00
11	OC_	N11	51.728	41.572	15.438	0.00
12	OC_	C12	50.628	41.640	14.622	0.00
13	OC_	O13	50.068	42.623	14.140	0.00
14	OC_	O14	52.998	39.925	16.291	0.00
15	OC_	O15	51.718	37.289	15.246	0.00
16	OC_	H16	51.994	36.801	14.488	0.00
17	OC_	C17	52.602	42.662	15.945	0.00
18	OC_	C18	51.989	43.758	16.830	0.00

19	OC_	H19	53.162	43.136	15.129	0.00
20	OC_	H20	53.441	42.237	16.493	0.00
21	OC_	O21	52.823	43.764	17.935	0.00
22	OC_	C22	52.911	44.965	18.630	0.00
23	OC_	C23	51.464	45.106	19.104	0.00
24	OC_	C24	50.401	44.489	18.575	0.00
25	OC_	C25	50.577	43.599	17.383	0.00
26	OC_	6H2	52.083	44.717	16.324	0.00
27	OC_	H27	53.299	45.778	18.011	0.00
28	OC_	H28	53.618	44.846	19.458	0.00
29	OC_	9H2	49.817	43.779	16.639	0.00
30	OC_	0H3	50.512	42.573	17.745	0.00
31	OC_	S31	50.995	45.860	20.622	0.00
32	OC_	C32	49.309	45.615	20.276	0.00
33	OC_	C33	49.082	44.948	19.126	0.00
34	OC_	N34	48.236	46.161	21.034	0.00
35	OC_	C35	48.405	46.833	22.220	0.00
36	OC_	C36	47.021	47.267	22.889	0.00
37	OC_	O37	46.749	48.354	23.338	0.00
38	OC_	O38	46.116	46.291	23.042	0.00
39	OC_	O39	49.477	47.023	22.820	0.00
40	OC_	C40	47.697	44.874	18.500	0.00
41	OC_	O41	46.650	44.969	19.070	0.00
42	OC_	O42	47.614	44.562	17.174	0.00
43	OC_	3H4	46.996	43.859	17.092	0.00
44	OC_	H44	45.261	46.650	23.184	0.00
45	OC_	H45	47.336	46.168	20.596	0.00
1	TIP	OH2	55.419	44.829	16.389	20.00
2	TIP	H1	55.536	44.889	17.342	20.00
3	TIP	2H	55.300	45.765	16.164	20.00
4	TIP	OH2	50.936	38.099	22.176	20.00
5	TIP	1H	51.119	38.023	23.113	20.00
6	TIP	H2	50.913	39.042	22.012	20.00
7	TIP	OH2	29.774	30.704	38.242	20.00
8	TIP	1H	29.956	30.628	39.179	20.00
9	TIP	H2	29.750	31.647	38.078	20.00
10	TIP	OH2	45.277	35.890	28.823	20.00
11	TIP	1H	45.460	35.813	29.759	20.00
12	TIP	H2	45.253	36.832	28.659	20.00
13	TIP	OH2	58.027	40.785	28.285	20.00
14	TIP	1H	58.210	40.709	29.222	20.00
15	TIP	H2	58.004	41.728	28.121	20.00
16	TIP	OH2	40.267	36.083	19.326	20.00
17	TIP	H1	40.450	36.007	20.263	20.00
18	TIP	2H	40.244	37.026	19.162	20.00
19	TIP	OH2	53.647	32.258	38.649	20.00
20	TIP	1H	53.830	32.182	39.585	20.00
21	TIP	H2	53.623	33.200	38.484	20.00
22	TIP	OH2	48.317	32.381	26.654	20.00
23	TIP	1H	48.499	32.305	27.591	20.00
24	TIP	H2	48.293	33.324	26.490	20.00
25	TIP	OH2	38.532	50.364	24.358	20.00

26	TIP	1H	38.714	50.288	25.294	20.00
27	TIP	H2	38.508	51.307	24.194	20.00
28	TIP	OH2	43.205	42.135	42.424	20.00
29	TIP	1H	43.387	42.059	43.360	20.00
30	TIP	2H	43.181	43.078	42.260	20.00
31	TIP	OH2	38.345	49.997	21.607	20.00
32	TIP	H1	38.528	49.921	22.543	20.00
33	TIP	H2	38.321	50.940	21.443	20.00
34	TIP	OH2	48.352	30.997	37.771	20.00
35	TIP	1H	48.535	30.921	38.708	20.00
36	TIP	H2	48.329	31.940	37.607	20.00
37	TIP	OH2	48.526	24.351	23.768	20.00
38	TIP	H1	48.709	24.275	24.705	20.00
39	TIP	2H	48.502	25.294	23.604	20.00
40	TIP	OH2	30.895	32.557	49.007	20.00
41	TIP	H1	31.078	32.480	49.944	20.00
42	TIP	2H	30.871	33.499	48.843	20.00
43	TIP	OH2	48.519	50.061	21.813	20.00
44	TIP	H1	48.702	49.985	22.750	20.00
45	TIP	2H	48.495	51.003	21.649	20.00
46	TIP	OH2	57.848	51.344	42.042	20.00
47	TIP	H1	58.031	51.268	42.978	20.00
48	TIP	2H	57.825	52.287	41.877	20.00
49	TIP	OH2	54.834	35.583	21.192	20.00
50	TIP	1H	55.017	35.507	22.129	20.00
51	TIP	H2	54.811	36.525	21.028	20.00
52	TIP	OH2	21.604	40.670	37.071	20.00
53	TIP	H1	21.787	40.594	38.007	20.00
54	TIP	2H	21.581	41.613	36.907	20.00
55	TIP	OH2	61.252	32.808	37.483	20.00
56	TIP	H1	61.435	32.732	38.420	20.00
57	TIP	2H	61.229	33.751	37.319	20.00
58	TIP	OH2	66.912	49.122	40.151	20.00
59	TIP	H1	67.094	49.046	41.088	20.00
60	TIP	2H	66.888	50.065	39.987	20.00
61	TIP	OH2	23.155	25.413	25.818	20.00
62	TIP	H1	23.337	25.337	26.755	20.00
63	TIP	2H	23.131	26.355	25.654	20.00
64	TIP	OH2	52.477	58.511	18.314	20.00
65	TIP	H1	52.659	58.434	19.250	20.00
66	TIP	2H	52.453	59.453	18.150	20.00
67	TIP	OH2	33.877	44.186	23.766	20.00
68	TIP	1H	34.060	44.110	24.702	20.00
69	TIP	H2	33.853	45.129	23.602	20.00
70	TIP	OH2	36.071	53.377	48.280	20.00
71	TIP	H1	36.254	53.301	49.216	20.00
72	TIP	2H	36.047	54.320	48.116	20.00
73	TIP	OH2	57.951	22.393	22.291	20.00
74	TIP	1H	58.133	22.317	23.228	20.00
75	TIP	H2	57.927	23.335	22.127	20.00
76	TIP	OH2	43.946	30.374	44.700	20.00
77	TIP	1H	44.128	30.298	45.637	20.00

78	TIP	H2	43.922	31.316	44.536	20.00
79	TIP	OH2	23.284	48.767	33.067	20.00
80	TIP	1H	23.466	48.691	34.004	20.00
81	TIP	H2	23.260	49.710	32.903	20.00
82	TIP	OH2	34.465	36.411	46.836	20.00
83	TIP	1H	34.648	36.335	47.773	20.00
84	TIP	H2	34.441	37.353	46.672	20.00
85	TIP	OH2	47.183	59.524	19.471	20.00
86	TIP	H1	47.365	59.448	20.407	20.00
87	TIP	2H	47.159	60.467	19.307	20.00
88	TIP	OH2	38.194	26.639	27.880	20.00
89	TIP	1H	38.377	26.563	28.816	20.00
90	TIP	H2	38.170	27.581	27.716	20.00
91	TIP	OH2	63.749	46.405	40.207	20.00
92	TIP	1H	63.932	46.329	41.143	20.00
93	TIP	H2	63.726	47.347	40.043	20.00
94	TIP	OH2	38.952	29.220	51.044	20.00
95	TIP	1H	39.135	29.144	51.980	20.00
96	TIP	H2	38.928	30.162	50.880	20.00
97	TIP	OH2	22.585	40.880	29.562	20.00
98	TIP	H1	22.768	40.804	30.498	20.00
99	TIP	2H	22.562	41.823	29.398	20.00
100	TIP	OH2	60.690	27.339	33.408	20.00
101	TIP	1H	60.873	27.263	34.345	20.00
102	TIP	H2	60.666	28.282	33.244	20.00
103	TIP	OH2	44.387	24.820	39.848	20.00
104	TIP	H1	44.570	24.744	40.784	20.00
105	TIP	H2	44.363	25.763	39.684	20.00
106	TIP	OH2	47.685	57.349	44.874	20.00
107	TIP	1H	47.867	57.272	45.810	20.00
108	TIP	H2	47.661	58.291	44.710	20.00
109	TIP	OH2	67.071	45.345	34.784	20.00
110	TIP	H1	67.254	45.268	35.720	20.00
111	TIP	2H	67.047	46.287	34.620	20.00
112	TIP	OH2	45.116	59.190	18.168	20.00
113	TIP	H1	45.298	59.114	19.105	20.00
114	TIP	2H	45.092	60.133	18.004	20.00
115	TIP	OH2	60.283	64.299	18.011	20.00
116	TIP	H1	60.466	64.223	18.947	20.00
117	TIP	2H	60.259	65.241	17.847	20.00
118	TIP	OH2	60.415	30.584	33.261	20.00
119	TIP	H1	60.598	30.508	34.198	20.00
120	TIP	2H	60.392	31.527	33.097	20.00
121	TIP	OH2	60.024	47.287	40.698	20.00
122	TIP	1H	60.207	47.211	41.634	20.00
123	TIP	H2	60.001	48.230	40.534	20.00
124	TIP	OH2	37.196	38.650	46.459	20.00
125	TIP	H1	37.379	38.574	47.395	20.00
126	TIP	2H	37.172	39.592	46.294	20.00
127	TIP	OH2	46.215	64.400	22.087	20.00
128	TIP	H1	46.398	64.324	23.024	20.00
129	TIP	2H	46.191	65.343	21.923	20.00

130	TIP	OH2	32.296	42.095	24.175	20.00
131	TIP	H1	32.479	42.019	25.112	20.00
132	TIP	2H	32.272	43.038	24.011	20.00
133	TIP	OH2	25.133	25.020	39.586	20.00
134	TIP	1H	25.316	24.944	40.523	20.00
135	TIP	2H	25.109	25.962	39.422	20.00
136	TIP	OH2	63.940	65.238	29.552	20.00
137	TIP	1H	64.123	65.162	30.489	20.00
138	TIP	H2	63.917	66.181	29.388	20.00
139	TIP	OH2	42.953	24.320	36.755	20.00
140	TIP	H1	43.135	24.244	37.692	20.00
141	TIP	2H	42.929	25.263	36.591	20.00
142	TIP	OH2	31.728	20.196	39.928	20.00
143	TIP	1H	31.910	20.120	40.864	20.00
144	TIP	H2	31.704	21.139	39.764	20.00
145	TIP	OH2	63.074	44.498	42.664	20.00
146	TIP	H1	63.256	44.422	43.600	20.00
147	TIP	H2	63.050	45.441	42.500	20.00
148	TIP	OH2	57.929	49.570	22.490	20.00
149	TIP	1H	58.112	49.494	23.426	20.00
150	TIP	2H	57.906	50.513	22.325	20.00
151	TIP	OH2	37.261	57.330	21.133	20.00
152	TIP	1H	37.444	57.254	22.070	20.00
153	TIP	2H	37.238	58.273	20.969	20.00
154	TIP	OH2	49.491	44.986	44.949	20.00
155	TIP	H1	49.673	44.910	45.886	20.00
156	TIP	2H	49.467	45.929	44.785	20.00
157	TIP	OH2	58.235	25.415	34.562	20.00
158	TIP	1H	58.417	25.339	35.498	20.00
159	TIP	H2	58.211	26.358	34.398	20.00
160	TIP	OH2	39.581	24.265	39.192	20.00
161	TIP	H1	39.763	24.189	40.129	20.00
162	TIP	2H	39.557	25.208	39.028	20.00
163	TIP	OH2	26.644	29.865	39.722	20.00
164	TIP	H1	26.827	29.789	40.658	20.00
165	TIP	2H	26.620	30.807	39.558	20.00
166	TIP	OH2	46.323	43.759	44.595	20.00
167	TIP	H1	46.506	43.683	45.532	20.00
168	TIP	2H	46.300	44.701	44.431	20.00

TABLE D

Table of the orthogonal three dimensional coordinates in Ångstroms and B factors (Å^2) for Protein Tyrosine Phosphatase 1B complexed with 2-(oxalyl-amino)-7-(1,1,3-trioxo-1*H*-benzo[d]isothiazol-3-yloxomethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxylic acid and the water molecule which forms hydrogen bonds with the pyran oxygen atom, the side chain oxygen atom and aspartic acid 48 (Example XX).

No	Amino acid		X	Y	Z	B
1	GLU	N	21.703	70.016	37.889	44.68
2	GLU	CA	20.473	69.206	37.782	43.88
3	GLU	C	20.313	68.401	36.438	42.17
4	GLU	O	20.963	68.696	35.441	41.34
5	GLU	CB	19.333	70.227	37.986	46.14
6	GLU	CG	17.913	69.694	38.169	53.54
7	GLU	CD	17.723	68.479	39.088	61.73
8	GLU	OE1	16.693	68.363	39.735	64.31
9	GLU	OE2	18.581	67.618	39.170	63.66
10	MET	N	19.366	67.432	36.416	39.32
11	MET	CA	18.893	66.684	35.226	34.55
12	MET	C	18.088	67.589	34.297	32.30
13	MET	O	18.046	67.444	33.093	32.26
14	MET	CB	17.971	65.501	35.627	34.25
15	MET	CG	16.763	65.884	36.525	32.80
16	MET	SD	15.642	64.525	36.918	29.12
17	MET	CE	16.780	63.485	37.833	28.64
18	GLU	N	17.444	68.545	34.943	32.02
19	GLU	CA	16.660	69.568	34.282	35.48
20	GLU	C	17.565	70.545	33.478	34.80
21	GLU	O	17.324	70.861	32.328	34.07
22	GLU	CB	15.843	70.226	35.377	37.66
23	GLU	CG	14.638	71.016	34.859	41.16
24	GLU	CD	13.640	71.228	36.010	44.68
25	GLU	OE1	14.018	71.066	37.168	43.98
26	GLU	OE2	12.488	71.540	35.734	47.38
27	LYS	N	18.704	70.909	34.098	35.30
28	LYS	CA	19.749	71.591	33.318	36.11
29	LYS	C	20.297	70.750	32.115	33.14
30	LYS	O	20.337	71.206	30.978	32.17
31	LYS	CB	20.887	72.023	34.258	40.81
32	LYS	CG	20.524	73.209	35.174	47.76
33	LYS	CD	21.621	73.495	36.226	53.62
34	LYS	CE	21.051	73.908	37.587	55.86
35	LYS	NZ	21.885	73.368	38.677	56.39
36	GLU	N	20.701	69.500	32.404	31.78
37	GLU	CA	21.112	68.597	31.321	30.77
38	GLU	C	20.053	68.489	30.194	30.69
39	GLU	O	20.353	68.592	29.020	29.85

40	GLU	CB	21.406	67.217	31.894	32.53
41	GLU	CG	21.384	66.134	30.814	37.49
42	GLU	CD	22.178	64.888	31.173	38.32
43	GLU	OE1	22.206	64.433	32.300	42.27
44	GLU	OE2	22.785	64.379	30.267	40.62
45	PHE	N	18.794	68.321	30.587	30.73
46	PHE	CA	17.727	68.276	29.603	32.45
47	PHE	C	17.750	69.480	28.642	34.85
48	PHE	O	17.904	69.288	27.453	33.64
49	PHE	CB	16.381	68.223	30.320	30.35
50	PHE	CG	15.294	67.870	29.350	26.13
51	PHE	CD1	15.021	66.538	29.085	25.00
52	PHE	CD2	14.582	68.860	28.688	22.62
53	PHE	CE1	14.068	66.173	28.147	24.45
54	PHE	CE2	13.636	68.508	27.740	23.14
55	PHE	CZ	13.391	67.166	27.459	23.15
56	GLU	N	17.650	70.698	29.207	38.88
57	GLU	CA	17.603	71.927	28.405	42.49
58	GLU	C	18.812	71.977	27.485	40.63
59	GLU	O	18.782	72.264	26.313	38.60
60	GLU	CB	17.758	73.128	29.336	48.61
61	GLU	CG	16.586	73.249	30.307	59.10
62	GLU	CD	15.360	73.806	29.606	67.27
63	GLU	OE1	15.504	74.386	28.522	72.82
64	GLU	OE2	14.274	73.680	30.153	69.58
65	GLN	N	19.926	71.681	28.084	38.72
66	GLN	CA	21.182	71.677	27.384	39.05
67	GLN	C	21.295	70.629	26.263	36.85
68	GLN	O	21.920	70.876	25.239	37.31
69	GLN	CB	22.160	71.459	28.488	43.39
70	GLN	CG	23.600	71.228	28.046	51.02
71	GLN	CD	24.424	70.842	29.287	57.42
72	GLN	OE1	25.562	70.436	29.224	62.88
73	GLN	NE2	23.787	70.955	30.441	59.65
74	ILE	N	20.644	69.479	26.488	33.52
75	ILE	CA	20.568	68.460	25.480	28.82
76	ILE	C	19.654	68.921	24.295	27.31
77	ILE	O	19.969	68.894	23.110	27.61
78	ILE	CB	20.239	67.069	25.944	27.67
79	ILE	CG1	21.327	66.546	26.867	25.62
80	ILE	CG2	20.110	66.093	24.775	24.46
81	ILE	CD1	20.897	65.251	27.523	28.44
82	ASP	N	18.496	69.346	24.737	27.29
83	ASP	CA	17.539	69.884	23.816	28.22
84	ASP	C	18.093	71.055	22.974	29.77
85	ASP	O	17.950	71.106	21.763	29.46
86	ASP	CB	16.329	70.307	24.644	26.78
87	ASP	CG	15.094	69.454	24.346	25.32
88	ASP	OD1	15.182	68.402	23.784	25.41
89	ASP	OD2	14.023	69.884	24.659	25.96
90	LYS	N	18.772	71.968	23.654	34.04
91	LYS	CA	19.284	73.163	23.027	38.17

92	LYS	C	20.201	72.782	21.859	38.28
93	LYS	O	20.020	73.189	20.713	41.49
94	LYS	CB	20.015	74.041	24.063	43.91
95	LYS	CG	19.071	74.819	25.012	52.90
96	LYS	CD	19.799	75.829	25.904	58.71
97	LYS	CE	18.834	76.499	26.900	60.27
98	LYS	NZ	19.587	77.453	27.717	61.96
99	SER	N	21.163	71.912	22.177	35.28
100	SER	CA	22.098	71.545	21.090	33.50
101	SER	C	21.511	70.377	20.261	33.89
102	SER	O	22.246	69.714	19.554	35.89
103	SER	CB	23.342	70.937	21.788	32.34
104	SER	OG	22.978	69.903	22.780	34.77
105	GLY	N	20.201	70.097	20.417	32.04
106	GLY	CA	19.593	68.985	19.695	31.04
107	GLY	C	20.362	67.670	19.728	31.12
108	GLY	O	20.378	66.986	18.724	34.31
109	SER	N	20.977	67.282	20.858	29.06
110	SER	CA	21.777	66.031	20.725	26.56
111	SER	C	21.199	64.762	21.398	25.00
112	SER	O	21.940	63.835	21.667	26.10
113	SER	CB	23.233	66.335	21.115	28.79
114	SER	OG	23.361	67.063	22.382	32.58
115	TRP	N	19.855	64.639	21.554	22.56
116	TRP	CA	19.293	63.388	22.093	19.31
117	TRP	C	19.786	62.100	21.381	18.55
118	TRP	O	20.083	61.102	22.013	20.55
119	TRP	CB	17.751	63.440	22.080	17.74
120	TRP	CG	17.247	64.345	23.180	17.53
121	TRP	CD1	16.779	65.654	23.022	14.15
122	TRP	CD2	17.312	64.085	24.605	16.03
123	TRP	NE1	16.593	66.177	24.251	16.66
124	TRP	CE2	16.887	65.268	25.251	17.66
125	TRP	CE3	17.675	63.004	25.350	11.39
126	TRP	CZ2	16.898	65.347	26.623	18.08
127	TRP	CZ3	17.676	63.059	26.745	10.09
128	TRP	CH2	17.279	64.235	27.383	15.36
129	ALA	N	19.871	62.143	20.056	17.72
130	ALA	CA	20.202	60.910	19.307	17.15
131	ALA	C	21.652	60.428	19.547	15.94
132	ALA	O	21.895	59.243	19.607	16.09
133	ALA	CB	20.042	61.212	17.815	15.04
134	ALA	N	22.583	61.369	19.645	15.86
135	ALA	CA	23.953	61.087	20.057	16.56
136	ALA	C	24.062	60.639	21.520	17.32
137	ALA	O	24.632	59.609	21.781	18.09
138	ALA	CB	24.761	62.357	19.906	14.93
139	ILE	N	23.417	61.377	22.433	17.87
140	ILE	CA	23.245	60.832	23.789	19.03
141	ILE	C	22.763	59.345	23.796	18.11
142	ILE	O	23.305	58.438	24.409	18.57
143	ILE	CB	22.216	61.696	24.560	21.02

144	ILE	CG1	22.665	63.159	24.647	20.66
145	ILE	CG2	22.012	61.186	25.992	20.04
146	ILE	CD1	24.097	63.283	25.120	18.89
147	TYR	N	21.674	59.132	23.082	16.17
148	TYR	CA	21.120	57.794	23.060	17.24
149	TYR	C	22.043	56.788	22.376	19.36
150	TYR	O	22.300	55.706	22.907	19.20
151	TYR	CB	19.754	57.851	22.383	15.19
152	TYR	CG	19.119	56.501	22.280	15.92
153	TYR	CD1	18.853	55.782	23.434	14.65
154	TYR	CD2	18.790	55.967	21.035	16.31
155	TYR	CE1	18.267	54.556	23.417	13.96
156	TYR	CE2	18.159	54.733	20.979	14.00
157	TYR	CZ	17.905	54.008	22.163	14.32
158	TYR	OH	17.345	52.759	21.944	11.00
159	GLN	N	22.561	57.160	21.194	21.20
160	GLN	CA	23.605	56.331	20.588	24.13
161	GLN	C	24.713	56.001	21.593	21.45
162	GLN	O	25.184	54.880	21.631	20.37
163	GLN	CB	24.248	56.982	19.353	34.41
164	GLN	CG	25.321	56.035	18.773	49.84
165	GLN	CD	26.136	56.556	17.565	62.54
166	GLN	OE1	26.977	55.883	16.989	66.64
167	GLN	NE2	25.813	57.794	17.172	67.57
168	ASP	N	25.085	57.002	22.391	21.19
169	ASP	CA	26.174	56.832	23.339	23.68
170	ASP	C	25.858	55.716	24.328	23.38
171	ASP	O	26.600	54.749	24.489	24.87
172	ASP	CB	26.451	58.140	24.079	28.19
173	ASP	CG	27.103	59.205	23.199	31.40
174	ASP	OD1	27.483	58.905	22.061	34.52
175	ASP	OD2	27.221	60.349	23.646	34.31
176	ILE	N	24.627	55.828	24.873	21.79
177	ILE	CA	24.154	54.745	25.716	20.54
178	ILE	C	24.220	53.381	24.999	20.53
179	ILE	O	24.664	52.384	25.562	19.96
180	ILE	CB	22.722	55.057	26.188	19.90
181	ILE	CG1	22.746	56.121	27.295	18.92
182	ILE	CG2	22.002	53.809	26.709	13.13
183	ILE	CD1	21.427	56.904	27.348	23.15
184	ARG	N	23.711	53.345	23.741	20.41
185	ARG	CA	23.715	52.099	22.985	22.09
186	ARG	C	25.141	51.469	22.930	23.43
187	ARG	O	25.286	50.258	23.023	21.33
188	ARG	CB	23.088	52.300	21.584	24.59
189	ARG	CG	21.532	52.302	21.526	27.48
190	ARG	CD	20.912	52.327	20.101	32.84
191	ARG	NE	19.450	52.168	20.157	43.35
192	ARG	CZ	18.645	51.724	19.167	44.57
193	ARG	NH1	19.112	51.575	17.953	46.24
194	ARG	NH2	17.395	51.443	19.393	38.15
195	HIS	N	26.156	52.353	22.819	26.24

196	HIS	CA	27.538	51.876	22.706	29.54
197	HIS	C	28.137	51.358	24.001	30.14
198	HIS	O	28.822	50.348	24.027	31.41
199	HIS	CB	28.432	52.975	22.150	35.11
200	HIS	CG	28.242	52.899	20.676	45.77
201	HIS	ND1	28.436	51.769	19.968	50.82
202	HIS	CD2	27.726	53.883	19.830	48.72
203	HIS	CE1	28.026	52.047	18.726	53.20
204	HIS	NE2	27.594	53.318	18.613	51.96
205	GLU	N	27.850	52.116	25.059	29.74
206	GLU	CA	28.217	51.750	26.423	26.86
207	GLU	C	27.461	50.503	26.956	25.10
208	GLU	O	27.958	49.784	27.824	25.66
209	GLU	CB	27.885	52.987	27.258	29.73
210	GLU	CG	28.749	54.190	26.816	36.62
211	GLU	CD	28.227	55.576	27.238	42.17
212	GLU	OE1	27.415	55.678	28.155	43.56
213	GLU	OE2	28.663	56.549	26.634	42.82
214	ALA	N	26.224	50.276	26.460	22.66
215	ALA	CA	25.424	49.170	27.037	19.17
216	ALA	C	26.192	47.808	27.064	17.78
217	ALA	O	27.027	47.515	26.229	18.91
218	ALA	CB	24.115	49.032	26.262	11.88
219	SER	N	25.866	47.002	28.076	16.59
220	SER	CA	26.466	45.670	28.261	15.02
221	SER	C	26.067	44.661	27.239	15.21
222	SER	O	25.057	44.724	26.572	14.30
223	SER	CB	25.928	45.219	29.658	13.45
224	SER	OG	26.076	46.179	30.730	20.52
225	ASP	N	26.914	43.640	27.200	18.46
226	ASP	CA	26.637	42.515	26.346	18.64
227	ASP	C	27.079	41.224	27.054	16.04
228	ASP	O	28.233	41.010	27.385	17.44
229	ASP	CB	27.372	42.760	25.036	23.76
230	ASP	CG	26.832	41.802	23.989	28.93
231	ASP	OD1	25.701	41.295	24.133	29.41
232	ASP	OD2	27.537	41.564	23.023	33.21
233	PHE	N	26.075	40.401	27.320	14.88
234	PHE	CA	26.312	39.115	27.938	12.14
235	PHE	C	25.696	37.991	27.085	10.36
236	PHE	O	24.778	38.182	26.301	14.29
237	PHE	CB	25.708	39.121	29.344	9.41
238	PHE	CG	26.277	40.180	30.227	10.05
239	PHE	CD1	27.508	39.992	30.862	12.58
240	PHE	CD2	25.566	41.344	30.471	6.85
241	PHE	CE1	28.002	40.930	31.768	9.43
242	PHE	CE2	26.045	42.265	31.390	5.14
243	PHE	CZ	27.251	42.063	32.036	7.18
244	PRO	N	26.241	36.762	27.253	7.14
245	PRO	CA	25.755	35.675	26.473	6.52
246	PRO	C	24.277	35.394	26.679	9.69
247	PRO	O	23.748	35.569	27.762	12.15

248	PRO	CB	26.607	34.503	26.897	3.58
249	PRO	CG	27.467	34.928	28.059	4.26
250	PRO	CD	27.366	36.422	28.133	3.15
251	CYS	N	23.626	34.982	25.597	12.69
252	CYS	CA	22.261	34.498	25.720	14.65
253	CYS	C	22.172	33.102	25.112	17.19
254	CYS	O	21.342	32.783	24.256	16.47
255	CYS	CB	21.300	35.454	25.016	13.35
256	CYS	SG	21.382	37.237	25.396	15.48
257	ARG	N	23.129	32.258	25.541	18.46
258	ARG	CA	23.174	30.921	24.986	19.34
259	ARG	C	21.865	30.155	25.153	19.02
260	ARG	O	21.360	29.596	24.201	20.59
261	ARG	CB	24.339	30.190	25.590	24.24
262	ARG	CG	25.684	30.614	24.976	34.28
263	ARG	CD	26.506	31.531	25.846	42.36
264	ARG	NE	26.067	31.510	27.243	47.65
265	ARG	CZ	26.832	31.598	28.306	47.20
266	ARG	NH1	28.125	31.583	28.117	46.56
267	ARG	NH2	26.311	31.717	29.498	44.55
268	VAL	N	21.246	30.117	26.340	17.94
269	VAL	CA	20.046	29.252	26.364	16.39
270	VAL	C	18.870	29.732	25.445	16.62
271	VAL	O	18.228	28.961	24.769	20.22
272	VAL	CB	19.708	28.709	27.746	14.40
273	VAL	CG1	18.301	29.008	28.203	13.66
274	VAL	CG2	20.727	29.076	28.805	11.01
275	ALA	N	18.666	31.040	25.380	16.61
276	ALA	CA	17.795	31.721	24.438	13.61
277	ALA	C	18.036	31.352	23.035	12.12
278	ALA	O	17.160	31.403	22.187	12.55
279	ALA	CB	18.080	33.255	24.451	10.37
280	LYS	N	19.303	31.043	22.828	11.81
281	LYS	CA	19.667	30.701	21.490	12.07
282	LYS	C	19.712	29.217	21.190	13.74
283	LYS	O	19.996	28.858	20.061	17.30
284	LYS	CB	20.968	31.391	21.154	12.40
285	LYS	CG	20.822	32.884	20.934	13.01
286	LYS	CD	19.574	33.099	20.085	17.78
287	LYS	CE	19.498	34.385	19.324	22.14
288	LYS	NZ	18.143	34.532	18.753	25.46
289	LEU	N	19.358	28.374	22.149	13.01
290	LEU	CA	19.324	26.958	21.822	13.50
291	LEU	C	18.159	26.587	20.853	16.14
292	LEU	O	17.057	27.133	20.907	14.24
293	LEU	CB	19.105	26.163	23.118	11.77
294	LEU	CG	20.222	26.230	24.139	8.45
295	LEU	CD1	21.462	25.514	23.666	2.00
296	LEU	CD2	19.752	25.632	25.474	5.67
297	PRO	N	18.411	25.594	19.966	18.99
298	PRO	CA	17.420	25.201	18.974	20.81
299	PRO	C	16.038	24.817	19.486	21.23

300	PRO	O	15.028	25.094	18.853	23.12
301	PRO	CB	18.053	23.970	18.312	22.01
302	PRO	CG	19.544	24.226	18.419	20.31
303	PRO	CD	19.693	24.935	19.760	21.95
304	LYS	N	16.032	24.245	20.703	20.72
305	LYS	CA	14.730	23.878	21.253	20.41
306	LYS	C	13.860	25.101	21.665	22.87
307	LYS	O	12.648	25.010	21.812	25.57
308	LYS	CB	14.945	22.949	22.437	19.35
309	LYS	CG	15.755	23.579	23.575	18.95
310	LYS	CD	15.710	22.689	24.822	21.88
311	LYS	CE	16.801	23.034	25.823	28.88
312	LYS	NZ	16.535	22.399	27.128	34.05
313	ASN	N	14.556	26.233	21.841	20.66
314	ASN	CA	13.870	27.431	22.279	18.39
315	ASN	C	13.486	28.352	21.122	18.29
316	ASN	O	12.970	29.444	21.354	16.34
317	ASN	CB	14.739	28.164	23.298	16.54
318	ASN	CG	14.821	27.389	24.621	18.02
319	ASN	OD1	13.969	26.599	24.993	18.28
320	ASN	ND2	15.875	27.678	25.307	15.54
321	LYS	N	13.754	27.923	19.857	19.25
322	LYS	CA	13.464	28.846	18.745	20.87
323	LYS	C	12.043	29.452	18.860	18.97
324	LYS	O	11.823	30.654	18.781	18.79
325	LYS	CB	13.693	28.184	17.377	25.70
326	LYS	CG	14.211	29.179	16.316	33.55
327	LYS	CD	14.555	28.542	14.949	41.05
328	LYS	CE	15.066	29.579	13.926	44.78
329	LYS	NZ	14.971	29.087	12.537	44.25
330	ASN	N	11.091	28.544	19.113	15.61
331	ASN	CA	9.708	28.969	19.134	14.25
332	ASN	C	9.210	29.512	20.495	13.55
333	ASN	O	8.012	29.666	20.711	11.55
334	ASN	CB	8.855	27.796	18.681	14.58
335	ASN	CG	8.704	26.756	19.791	18.11
336	ASN	OD1	9.204	26.857	20.899	19.64
337	ASN	ND2	7.912	25.772	19.462	22.97
338	ARG	N	10.163	29.703	21.400	12.38
339	ARG	CA	9.830	30.375	22.640	12.69
340	ARG	C	10.255	31.846	22.554	11.47
341	ARG	O	10.045	32.608	23.480	10.92
342	ARG	CB	10.492	29.633	23.827	12.58
343	ARG	CG	9.840	28.263	24.143	7.25
344	ARG	CD	10.452	27.622	25.391	6.96
345	ARG	NE	9.754	26.378	25.717	10.56
346	ARG	CZ	9.591	25.939	26.964	12.63
347	ARG	NH1	10.049	26.621	27.978	13.70
348	ARG	NH2	8.970	24.830	27.205	13.18
349	ASN	N	10.877	32.231	21.416	11.45
350	ASN	CA	11.276	33.639	21.283	10.48
351	ASN	C	10.479	34.359	20.189	10.61

352	ASN	O	10.425	33.924	19.054	12.34
353	ASN	CB	12.749	33.695	20.923	9.53
354	ASN	CG	13.512	33.223	22.114	13.73
355	ASN	OD1	13.255	33.613	23.245	15.94
356	ASN	ND2	14.468	32.378	21.802	13.53
357	ARG	N	9.906	35.498	20.587	9.18
358	ARG	CA	9.132	36.240	19.605	7.77
359	ARG	C	9.980	36.947	18.540	6.85
360	ARG	O	9.628	37.017	17.379	6.50
361	ARG	CB	8.232	37.214	20.383	7.45
362	ARG	CG	7.408	38.017	19.428	5.78
363	ARG	CD	6.595	39.001	20.150	7.80
364	ARG	NE	5.520	38.392	20.894	7.84
365	ARG	CZ	4.356	38.086	20.319	6.71
366	ARG	NH1	4.093	38.311	19.075	3.66
367	ARG	NH2	3.466	37.541	21.012	3.47
368	TYR	N	11.110	37.522	18.982	8.09
369	TYR	CA	11.994	38.167	18.021	7.20
370	TYR	C	13.398	37.575	18.097	10.87
371	TYR	O	13.994	37.455	19.164	11.24
372	TYR	CB	12.115	39.628	18.386	5.76
373	TYR	CG	10.820	40.320	18.388	7.25
374	TYR	CD1	10.123	40.388	17.212	10.32
375	TYR	CD2	10.304	40.862	19.541	3.38
376	TYR	CE1	8.881	40.994	17.151	12.06
377	TYR	CE2	9.097	41.526	19.474	8.53
378	TYR	CZ	8.354	41.606	18.291	12.52
379	TYR	OH	7.116	42.223	18.267	12.22
380	ARG	N	13.917	37.304	16.886	12.71
381	ARG	CA	15.268	36.791	16.740	14.19
382	ARG	C	16.325	37.589	17.518	15.21
383	ARG	O	17.239	36.987	18.070	17.69
384	ARG	CB	15.618	36.796	15.242	16.20
385	ARG	CG	16.894	36.009	14.934	20.90
386	ARG	CD	17.513	36.381	13.600	24.13
387	ARG	NE	18.032	37.734	13.679	31.45
388	ARG	CZ	18.180	38.440	12.559	35.35
389	ARG	NH1	18.031	37.849	11.400	34.27
390	ARG	NH2	18.426	39.722	12.626	36.59
391	ASP	N	16.129	38.922	17.483	15.52
392	ASP	CA	17.068	39.945	17.947	14.40
393	ASP	C	16.939	40.307	19.430	12.23
394	ASP	O	17.780	41.001	19.966	11.34
395	ASP	CB	16.825	41.235	17.144	19.70
396	ASP	CG	17.502	41.193	15.756	24.49
397	ASP	OD1	18.205	40.237	15.418	27.69
398	ASP	OD2	17.350	42.135	14.999	25.18
399	VAL	N	15.836	39.831	20.061	13.80
400	VAL	CA	15.628	40.144	21.478	13.65
401	VAL	C	15.556	38.911	22.396	13.05
402	VAL	O	14.676	38.066	22.356	10.76
403	VAL	CB	14.512	41.187	21.704	14.37

404	VAL	CG1	13.751	41.144	23.012	10.38
405	VAL	CG2	13.935	41.930	20.498	12.19
406	SER	N	16.585	38.852	23.257	14.06
407	SER	CA	16.846	37.705	24.127	9.73
408	SER	C	17.249	38.159	25.487	8.28
409	SER	O	17.770	39.230	25.677	5.98
410	SER	CB	17.993	36.869	23.463	10.62
411	SER	OG	17.811	36.472	22.071	11.36
412	PRO	N	16.972	37.263	26.461	7.35
413	PRO	CA	17.450	37.352	27.792	8.44
414	PRO	C	18.908	36.905	27.921	11.00
415	PRO	O	19.259	35.821	27.503	13.36
416	PRO	CB	16.474	36.351	28.513	7.21
417	PRO	CG	16.182	35.277	27.531	11.53
418	PRO	CD	16.259	36.046	26.224	9.12
419	PHE	N	19.753	37.763	28.507	10.36
420	PHE	CA	21.035	37.197	28.928	8.56
421	PHE	C	20.847	35.981	29.853	10.75
422	PHE	O	19.894	35.899	30.634	12.42
423	PHE	CB	21.829	38.225	29.725	6.92
424	PHE	CG	21.969	39.566	29.090	4.90
425	PHE	CD1	22.372	39.651	27.773	2.00
426	PHE	CD2	21.749	40.718	29.841	3.60
427	PHE	CE1	22.581	40.893	27.214	3.30
428	PHE	CE2	21.964	41.964	29.276	2.19
429	PHE	CZ	22.390	42.047	27.962	2.00
430	ASP	N	21.804	35.056	29.764	11.92
431	ASP	CA	21.710	33.883	30.620	12.44
432	ASP	C	21.749	34.248	32.129	10.45
433	ASP	O	21.055	33.664	32.955	14.63
434	ASP	CB	22.852	32.934	30.260	13.15
435	ASP	CG	22.759	32.466	28.829	17.42
436	ASP	OD1	21.740	31.969	28.404	17.02
437	ASP	OD2	23.745	32.592	28.162	18.42
438	HIS	N	22.577	35.242	32.485	6.99
439	HIS	CA	22.781	35.415	33.933	7.65
440	HIS	C	21.522	35.922	34.692	11.47
441	HIS	O	21.329	35.728	35.891	12.59
442	HIS	CB	23.994	36.314	34.157	4.46
443	HIS	CG	23.699	37.794	34.137	5.10
444	HIS	ND1	23.259	38.489	35.219	8.84
445	HIS	CD2	23.892	38.696	33.091	5.96
446	HIS	CE1	23.198	39.775	34.852	5.13
447	HIS	NE2	23.568	39.921	33.577	7.85
448	SER	N	20.686	36.648	33.929	11.96
449	SER	CA	19.591	37.347	34.601	10.61
450	SER	C	18.221	36.722	34.179	11.50
451	SER	O	17.161	37.166	34.622	13.21
452	SER	CB	19.578	38.795	34.005	6.54
453	SER	OG	19.426	38.747	32.546	11.00
454	ARG	N	18.259	35.718	33.274	10.94
455	ARG	CA	16.999	35.170	32.768	12.70

456	ARG	C	16.139	34.506	33.898	14.39
457	ARG	O	16.647	33.926	34.844	12.31
458	ARG	CB	17.292	34.168	31.637	12.58
459	ARG	CG	17.894	32.846	32.135	14.19
460	ARG	CD	18.073	31.815	31.023	15.27
461	ARG	NE	18.531	30.520	31.560	15.37
462	ARG	CZ	17.720	29.463	31.683	15.74
463	ARG	NH1	16.468	29.566	31.330	13.61
464	ARG	NH2	18.150	28.339	32.167	13.65
465	ILE	N	14.811	34.584	33.745	16.19
466	ILE	CA	13.964	33.837	34.671	13.97
467	ILE	C	13.863	32.356	34.253	13.70
468	ILE	O	13.599	32.046	33.119	15.22
469	ILE	CB	12.583	34.496	34.725	14.29
470	ILE	CG1	12.697	35.981	35.109	14.68
471	ILE	CG2	11.695	33.761	35.745	14.23
472	ILE	CD1	12.768	36.193	36.625	11.53
473	LYS	N	14.079	31.452	35.184	15.41
474	LYS	CA	13.901	30.039	34.865	16.79
475	LYS	C	12.555	29.531	35.391	17.35
476	LYS	O	12.222	29.772	36.539	19.31
477	LYS	CB	14.952	29.273	35.664	17.97
478	LYS	CG	16.348	29.641	35.224	20.00
479	LYS	CD	17.342	28.756	35.923	21.07
480	LYS	CE	18.757	29.183	35.586	25.86
481	LYS	NZ	19.661	28.132	36.065	29.41
482	LEU	N	11.827	28.807	34.546	17.14
483	LEU	CA	10.659	28.096	35.026	16.17
484	LEU	C	11.101	26.982	35.997	18.46
485	LEU	O	12.139	26.361	35.815	16.31
486	LEU	CB	9.925	27.512	33.820	16.73
487	LEU	CG	9.241	28.474	32.838	16.01
488	LEU	CD1	9.233	28.140	31.340	18.22
489	LEU	CD2	9.174	29.942	33.208	19.99
490	HIS	N	10.307	26.720	37.031	20.86
491	HIS	CA	10.504	25.539	37.856	22.12
492	HIS	C	9.967	24.256	37.160	26.50
493	HIS	O	9.214	23.488	37.729	29.06
494	HIS	CB	9.795	25.710	39.208	20.80
495	HIS	CG	10.244	26.940	39.961	18.49
496	HIS	ND1	9.650	27.355	41.096	18.74
497	HIS	CD2	11.279	27.836	39.657	17.16
498	HIS	CE1	10.306	28.462	41.471	16.79
499	HIS	NE2	11.293	28.776	40.626	15.80
500	GLN	N	10.416	24.000	35.928	31.86
501	GLN	CA	9.989	22.769	35.260	36.18
502	GLN	C	11.226	22.046	34.724	37.67
503	GLN	O	12.153	22.676	34.251	38.03
504	GLN	CB	8.969	23.068	34.141	38.37
505	GLN	CG	9.413	24.118	33.110	45.32
506	GLN	CD	8.538	24.115	31.844	51.67
507	GLN	OE1	8.913	23.628	30.781	53.74

508	GLN	NE2	7.325	24.611	32.016	51.04
509	GLU	N	11.195	20.711	34.825	40.34
510	GLU	CA	12.374	19.917	34.434	41.41
511	GLU	C	12.545	19.806	32.896	40.03
512	GLU	O	13.654	19.763	32.381	38.15
513	GLU	CB	12.223	18.535	35.054	45.95
514	GLU	CG	12.189	18.568	36.590	52.82
515	GLU	CD	11.488	17.315	37.138	60.20
516	GLU	OE1	11.234	16.382	36.370	63.99
517	GLU	OE2	11.181	17.291	38.322	61.75
518	ASP	N	11.382	19.779	32.207	39.83
519	ASP	CA	11.403	19.725	30.735	37.84
520	ASP	C	12.238	20.863	30.075	31.75
521	ASP	O	13.278	20.692	29.439	32.35
522	ASP	CB	9.941	19.774	30.258	45.12
523	ASP	CG	9.937	19.953	28.726	53.29
524	ASP	OD1	10.589	19.165	28.040	57.18
525	ASP	OD2	9.363	20.939	28.246	56.58
526	ASN	N	11.695	22.072	30.254	26.65
527	ASN	CA	12.390	23.201	29.678	21.86
528	ASN	C	12.099	24.449	30.528	20.05
529	ASN	O	11.018	25.025	30.494	21.82
530	ASN	CB	11.951	23.347	28.213	18.23
531	ASN	CG	12.778	24.425	27.560	15.37
532	ASN	OD1	13.328	25.282	28.216	19.18
533	ASN	ND2	12.889	24.375	26.266	5.53
534	ASP	N	13.138	24.890	31.233	17.24
535	ASP	CA	12.969	26.055	32.084	15.50
536	ASP	C	12.983	27.419	31.339	13.37
537	ASP	O	12.998	28.461	31.970	16.65
538	ASP	CB	14.049	26.012	33.173	19.65
539	ASP	CG	15.459	26.514	32.718	24.75
540	ASP	OD1	15.644	27.054	31.628	25.78
541	ASP	OD2	16.425	26.355	33.444	27.00
542	TYR	N	13.057	27.417	29.999	11.69
543	TYR	CA	13.282	28.673	29.271	9.17
544	TYR	C	11.981	29.477	29.069	8.95
545	TYR	O	10.979	28.944	28.618	10.59
546	TYR	CB	14.044	28.417	27.937	9.39
547	TYR	CG	14.285	29.690	27.182	7.68
548	TYR	CD1	15.282	30.541	27.605	5.47
549	TYR	CD2	13.461	30.068	26.121	6.70
550	TYR	CE1	15.383	31.821	27.085	6.80
551	TYR	CE2	13.539	31.330	25.557	5.20
552	TYR	CZ	14.498	32.243	26.073	8.53
553	TYR	OH	14.596	33.555	25.625	8.14
554	ILE	N	12.050	30.770	29.393	8.87
555	ILE	CA	11.093	31.830	29.070	10.50
556	ILE	C	11.899	33.107	28.707	10.84
557	ILE	O	12.881	33.469	29.342	11.65
558	ILE	CB	10.060	32.108	30.209	11.32

559	ILE	CG1	9.000	33.151	29.783	10.88
560	ILE	CG2	10.719	32.543	31.525	10.89
561	ILE	CD1	7.704	33.146	30.591	8.77
562	ASN	N	11.470	33.812	27.665	8.42
563	ASN	CA	12.083	35.065	27.316	8.86
564	ASN	C	11.668	36.151	28.345	8.99
565	ASN	O	10.725	36.902	28.126	9.36
566	ASN	CB	11.679	35.428	25.878	7.09
567	ASN	CG	12.506	36.595	25.383	7.69
568	ASN	OD1	12.723	37.602	26.057	9.31
569	ASN	ND2	12.964	36.408	24.164	4.12
570	ALA	N	12.428	36.178	29.455	7.57
571	ALA	CA	12.160	37.033	30.608	8.59
572	ALA	C	13.456	37.271	31.452	9.69
573	ALA	O	14.277	36.377	31.571	9.38
574	ALA	CB	11.128	36.326	31.528	8.05
575	SER	N	13.603	38.481	32.012	8.59
576	SER	CA	14.773	38.835	32.876	9.14
577	SER	C	14.389	39.499	34.110	10.33
578	SER	O	13.476	40.308	34.125	12.06
579	SER	CB	15.574	39.938	32.054	7.95
580	SER	OG	15.690	39.635	30.644	8.20
581	LEU	N	15.179	39.173	35.149	9.68
582	LEU	CA	15.021	39.922	36.386	10.62
583	LEU	C	15.923	41.152	36.334	9.94
584	LEU	O	17.141	41.081	36.377	10.46
585	LEU	CB	15.343	38.989	37.549	10.83
586	LEU	CG	15.005	39.449	38.990	13.92
587	LEU	CD1	13.816	40.385	39.226	12.88
588	LEU	CD2	16.114	39.506	40.027	12.99
589	ILE	N	15.258	42.299	36.213	10.44
590	ILE	CA	15.971	43.551	36.356	10.17
591	ILE	C	16.048	43.883	37.879	13.89
592	ILE	O	15.070	44.274	38.505	15.18
593	ILE	CB	15.228	44.651	35.596	8.61
594	ILE	CG1	15.428	44.579	34.073	6.44
595	ILE	CG2	15.734	46.015	36.078	10.00
596	ILE	CD1	15.155	43.216	33.468	5.57
597	LYS	N	17.239	43.734	38.432	15.52
598	LYS	CA	17.380	43.928	39.856	15.20
599	LYS	C	18.176	45.182	40.221	15.99
600	LYS	O	19.398	45.244	40.138	15.65
601	LYS	CB	18.123	42.725	40.331	18.92
602	LYS	CG	18.087	42.602	41.836	24.92
603	LYS	CD	18.365	41.191	42.268	32.15
604	LYS	CE	17.900	40.926	43.679	39.12
605	LYS	NZ	18.225	39.537	44.018	44.57
606	MET	N	17.397	46.178	40.655	15.97
607	MET	CA	17.988	47.464	40.974	16.08
608	MET	C	18.400	47.544	42.462	17.49
609	MET	O	17.579	47.794	43.332	17.67
610	MET	CB	16.968	48.533	40.607	14.83

611	MET	CG	16.626	48.573	39.119	13.99
612	MET	SD	18.121	48.583	38.091	17.00
613	MET	CE	18.404	50.363	38.012	4.51
614	GLU	N	19.696	47.328	42.741	19.80
615	GLU	CA	20.201	47.101	44.094	21.74
616	GLU	C	20.060	48.353	44.993	21.70
617	GLU	O	19.551	48.311	46.106	21.22
618	GLU	CB	21.652	46.627	44.007	24.29
619	GLU	CG	22.273	46.291	45.379	31.56
620	GLU	CD	23.780	45.945	45.252	36.04
621	GLU	OE1	24.575	46.709	44.678	39.83
622	GLU	OE2	24.167	44.887	45.726	40.03
623	GLU	N	20.500	49.491	44.427	22.15
624	GLU	CA	20.486	50.733	45.200	22.50
625	GLU	C	19.056	51.237	45.483	22.61
626	GLU	O	18.690	51.633	46.586	23.83
627	GLU	CB	21.321	51.751	44.448	23.01
628	GLU	CG	21.465	53.095	45.163	29.10
629	GLU	CD	21.921	54.170	44.157	35.50
630	GLU	OE1	21.836	53.969	42.942	36.25
631	GLU	OE2	22.346	55.218	44.595	38.56
632	ALA	N	18.218	51.181	44.432	23.89
633	ALA	CA	16.788	51.506	44.582	21.87
634	ALA	C	16.051	50.494	45.447	20.77
635	ALA	O	15.078	50.857	46.077	21.59
636	ALA	CB	16.112	51.586	43.207	19.61
637	GLN	N	16.555	49.262	45.482	22.52
638	GLN	CA	15.859	48.190	46.212	23.75
639	GLN	C	14.447	47.831	45.617	21.92
640	GLN	O	13.548	47.415	46.324	23.13
641	GLN	CB	15.781	48.573	47.700	28.00
642	GLN	CG	17.090	48.375	48.482	37.73
643	GLN	CD	17.102	46.993	49.161	45.98
644	GLN	OE1	16.962	46.865	50.359	49.70
645	GLN	NE2	17.222	45.958	48.347	46.64
646	ARG	N	14.293	47.996	44.288	19.87
647	ARG	CA	13.167	47.433	43.520	15.56
648	ARG	C	13.671	46.530	42.369	15.93
649	ARG	O	14.589	46.892	41.649	19.66
650	ARG	CB	12.378	48.566	42.894	12.31
651	ARG	CG	11.026	48.114	42.359	8.59
652	ARG	CD	9.975	49.222	42.284	8.75
653	ARG	NE	9.454	49.581	43.583	9.44
654	ARG	CZ	8.781	50.712	43.804	13.29
655	ARG	NH1	8.507	51.573	42.868	14.59
656	ARG	NH2	8.376	50.970	44.997	14.52
657	SER	N	13.018	45.374	42.191	13.03
658	SER	CA	13.174	44.563	40.969	11.10
659	SER	C	11.905	44.484	40.133	9.85
660	SER	O	10.797	44.430	40.625	7.17
661	SER	CB	13.491	43.098	41.352	9.97
662	SER	OG	14.257	42.832	42.565	16.33

663	TYR	N	12.149	44.304	38.838	10.99
664	TYR	CA	11.059	43.986	37.924	11.25
665	TYR	C	11.428	42.738	37.134	11.69
666	TYR	O	12.600	42.426	36.947	12.93
667	TYR	CB	10.855	45.145	36.944	11.85
668	TYR	CG	11.048	46.504	37.543	11.61
669	TYR	CD1	12.330	46.990	37.697	13.15
670	TYR	CD2	9.974	47.284	37.928	10.09
671	TYR	CE1	12.574	48.223	38.239	12.30
672	TYR	CE2	10.189	48.561	38.453	11.52
673	TYR	CZ	11.477	49.041	38.615	11.57
674	TYR	OH	11.518	50.318	39.128	16.85
675	ILE	N	10.411	42.065	36.626	10.13
676	ILE	CA	10.683	41.103	35.561	10.15
677	ILE	C	10.210	41.646	34.208	11.23
678	ILE	O	9.017	41.882	34.001	14.10
679	ILE	CB	9.984	39.783	35.918	8.65
680	ILE	CG1	10.575	39.226	37.221	5.54
681	ILE	CG2	10.117	38.788	34.758	4.72
682	ILE	CD1	9.885	37.981	37.750	3.41
683	LEU	N	11.171	41.837	33.292	8.83
684	LEU	CA	10.757	42.279	31.952	8.27
685	LEU	C	10.642	41.089	31.042	9.63
686	LEU	O	11.563	40.274	30.925	10.20
687	LEU	CB	11.754	43.266	31.361	6.64
688	LEU	CG	11.554	44.667	31.933	5.33
689	LEU	CD1	12.441	45.790	31.363	7.20
690	LEU	CD2	11.164	44.814	33.411	7.37
691	THR	N	9.476	41.020	30.372	9.19
692	THR	CA	9.353	39.941	29.424	7.94
693	THR	C	8.748	40.395	28.068	7.09
694	THR	O	8.236	41.487	27.941	6.68
695	THR	CB	8.633	38.725	30.140	7.51
696	THR	OG1	8.460	37.446	29.475	10.84
697	THR	CG2	7.202	39.098	30.532	4.90
698	GLN	N	8.895	39.560	27.025	5.28
699	GLN	CA	8.176	39.853	25.785	4.05
700	GLN	C	6.657	39.538	25.856	8.34
701	GLN	O	6.182	38.810	26.707	9.07
702	GLN	CB	8.778	38.943	24.733	4.35
703	GLN	CG	8.435	37.461	24.941	3.62
704	GLN	CD	9.043	36.521	23.968	7.57
705	GLN	OE1	8.588	35.441	23.735	13.92
706	GLN	NE2	10.151	36.927	23.436	7.22
707	GLY	N	5.886	40.050	24.882	8.61
708	GLY	CA	4.495	39.635	24.802	6.03
709	GLY	C	4.380	38.143	24.529	6.11
710	GLY	O	4.839	37.652	23.504	6.83
711	PRO	N	3.737	37.417	25.464	7.87
712	PRO	CA	3.639	35.977	25.333	7.10
713	PRO	C	3.212	35.542	23.927	8.95

714	PRO	O	2.432	36.210	23.249	9.13
715	PRO	CB	2.617	35.533	26.387	7.90
716	PRO	CG	2.452	36.716	27.320	8.31
717	PRO	CD	3.076	37.939	26.655	8.22
718	LEU	N	3.826	34.451	23.462	11.50
719	LEU	CA	3.453	33.772	22.222	12.63
720	LEU	C	2.284	32.817	22.537	10.92
721	LEU	O	2.099	32.425	23.675	10.18
722	LEU	CB	4.653	32.966	21.630	12.16
723	LEU	CG	5.658	33.617	20.677	10.05
724	LEU	CD1	7.130	33.604	21.085	9.84
725	LEU	CD2	5.220	34.724	19.751	8.39
726	PRO	N	1.493	32.446	21.503	11.77
727	PRO	CA	0.410	31.494	21.723	12.03
728	PRO	C	0.830	30.158	22.433	13.54
729	PRO	O	0.089	29.551	23.183	15.14
730	PRO	CB	-0.132	31.242	20.320	9.15
731	PRO	CG	0.277	32.454	19.478	10.31
732	PRO	CD	1.572	32.919	20.123	10.84
733	ASN	N	2.100	29.779	22.259	13.43
734	ASN	CA	2.585	28.584	22.964	13.13
735	ASN	C	3.324	28.859	24.291	11.81
736	ASN	O	3.962	27.974	24.845	11.04
737	ASN	CB	3.496	27.799	22.046	13.99
738	ASN	CG	4.657	28.667	21.597	16.96
739	ASN	OD1	4.503	29.783	21.131	22.38
740	ASN	ND2	5.839	28.120	21.783	18.79
741	THR	N	3.286	30.095	24.782	9.69
742	THR	CA	4.037	30.277	26.042	9.51
743	THR	C	3.210	31.147	27.020	11.20
744	THR	O	3.752	31.735	27.945	11.31
745	THR	CB	5.272	31.194	25.696	8.41
746	THR	OG1	4.946	32.545	25.282	10.58
747	THR	CG2	6.132	30.535	24.591	5.31
748	CYS	N	1.877	31.177	26.815	12.27
749	CYS	CA	1.007	31.799	27.822	12.45
750	CYS	C	0.947	30.973	29.109	12.47
751	CYS	O	0.771	31.526	30.183	14.18
752	CYS	CB	-0.422	32.004	27.341	8.19
753	CYS	SG	-0.524	32.997	25.849	9.18
754	GLY	N	1.156	29.654	28.975	10.77
755	GLY	CA	1.293	28.814	30.180	10.51
756	GLY	C	2.589	29.054	30.979	13.69
757	GLY	O	2.584	29.199	32.182	14.84
758	HIS	N	3.719	29.198	30.259	14.08
759	HIS	CA	4.993	29.584	30.868	11.53
760	HIS	C	4.914	30.988	31.502	11.94
761	HIS	O	5.482	31.244	32.554	14.08
762	HIS	CB	6.065	29.732	29.789	10.46
763	HIS	CG	6.166	28.534	28.894	10.11
764	HIS	ND1	6.494	28.651	27.599	10.39
765	HIS	CD2	5.952	27.176	29.154	10.94

766	HIS	CE1	6.495	27.433	27.054	9.44
767	HIS	NE2	6.173	26.529	27.977	9.56
768	PHE	N	4.216	31.925	30.815	9.75
769	PHE	CA	4.084	33.301	31.370	8.97
770	PHE	C	3.385	33.272	32.732	9.22
771	PHE	O	3.896	33.785	33.709	10.50
772	PHE	CB	3.365	34.218	30.386	7.25
773	PHE	CG	3.083	35.612	30.896	7.78
774	PHE	CD1	1.951	35.897	31.664	11.43
775	PHE	CD2	3.909	36.683	30.568	9.65
776	PHE	CE1	1.682	37.195	32.100	9.78
777	PHE	CE2	3.605	37.988	30.955	8.16
778	PHE	CZ	2.499	38.243	31.737	5.91
779	TRP	N	2.224	32.595	32.770	9.57
780	TRP	CA	1.478	32.437	34.017	9.40
781	TRP	C	2.170	31.539	35.067	10.21
782	TRP	O	2.124	31.827	36.254	12.41
783	TRP	CB	0.044	32.007	33.682	8.88
784	TRP	CG	-0.686	33.205	33.102	10.66
785	TRP	CD1	-1.211	33.295	31.810	11.90
786	TRP	CD2	-0.933	34.478	33.751	10.70
787	TRP	NE1	-1.748	34.526	31.630	13.39
788	TRP	CE2	-1.595	35.307	32.790	11.80
789	TRP	CE3	-0.672	34.978	35.004	10.81
790	TRP	CZ2	-1.912	36.601	33.125	9.91
791	TRP	CZ3	-1.002	36.282	35.341	6.82
792	TRP	CH2	-1.615	37.109	34.389	9.18
793	GLU	N	2.885	30.502	34.607	11.17
794	GLU	CA	3.798	29.745	35.468	8.99
795	GLU	C	4.825	30.644	36.135	8.16
796	GLU	O	4.957	30.683	37.347	10.61
797	GLU	CB	4.501	28.631	34.698	9.22
798	GLU	CG	5.405	27.764	35.612	10.50
799	GLU	CD	6.236	26.726	34.837	11.31
800	GLU	OE1	6.063	26.619	33.627	15.64
801	GLU	OE2	7.056	26.019	35.406	11.72
802	MET	N	5.477	31.465	35.308	6.74
803	MET	CA	6.436	32.428	35.835	7.30
804	MET	C	5.812	33.362	36.919	9.58
805	MET	O	6.404	33.616	37.963	11.01
806	MET	CB	7.044	33.189	34.659	4.95
807	MET	CG	7.808	34.437	35.117	8.57
808	MET	SD	8.586	35.351	33.769	10.82
809	MET	CE	7.136	36.296	33.246	5.07
810	VAL	N	4.592	33.892	36.686	11.04
811	VAL	CA	4.040	34.817	37.683	10.24
812	VAL	C	3.700	34.069	38.978	12.49
813	VAL	O	3.978	34.571	40.066	12.79
814	VAL	CB	2.754	35.438	37.092	8.52
815	VAL	CG1	2.812	36.052	35.686	3.31
816	VAL	CG2	1.750	36.088	38.062	6.62
817	TRP	N	3.107	32.838	38.856	13.65

818	TRP	CA	2.909	31.996	40.053	12.02
819	TRP	C	4.227	31.749	40.844	11.70
820	TRP	O	4.326	32.034	42.034	12.54
821	TRP	CB	2.217	30.672	39.710	10.42
822	TRP	CG	1.863	29.951	41.001	12.86
823	TRP	CD1	2.696	29.101	41.739	14.68
824	TRP	CD2	0.644	30.071	41.772	14.87
825	TRP	NE1	2.072	28.715	42.886	15.11
826	TRP	CE2	0.810	29.275	42.935	15.72
827	TRP	CE3	-0.539	30.710	41.553	15.15
828	TRP	CZ2	-0.194	29.217	43.858	16.05
829	TRP	CZ3	-1.558	30.644	42.477	14.60
830	TRP	CH2	-1.389	29.889	43.623	17.06
831	GLU	N	5.226	31.223	40.140	12.34
832	GLU	CA	6.504	30.890	40.783	13.26
833	GLU	C	7.246	32.102	41.352	15.44
834	GLU	O	7.808	32.021	42.444	18.46
835	GLU	CB	7.401	30.155	39.785	11.02
836	GLU	CG	6.906	28.742	39.525	9.86
837	GLU	CD	7.513	28.097	38.292	10.94
838	GLU	OE1	8.355	28.663	37.634	13.74
839	GLU	OE2	7.119	26.985	38.017	12.82
840	GLN	N	7.186	33.233	40.614	15.26
841	GLN	CA	7.871	34.449	41.042	15.75
842	GLN	C	7.052	35.265	42.051	16.17
843	GLN	O	7.555	36.199	42.665	16.73
844	GLN	CB	8.228	35.289	39.806	16.31
845	GLN	CG	9.155	34.556	38.822	16.92
846	GLN	CD	10.425	34.083	39.552	19.20
847	GLN	OE1	11.001	34.783	40.362	19.09
848	GLN	NE2	10.810	32.870	39.299	15.74
849	LYS	N	5.771	34.861	42.227	15.25
850	LYS	CA	4.934	35.484	43.254	13.27
851	LYS	C	4.651	36.977	42.993	13.03
852	LYS	O	4.524	37.792	43.895	10.75
853	LYS	CB	5.567	35.249	44.622	16.84
854	LYS	CG	5.787	33.755	44.877	20.72
855	LYS	CD	6.097	33.446	46.349	23.31
856	LYS	CE	6.774	32.099	46.522	26.45
857	LYS	NZ	7.947	31.999	45.619	30.79
858	SER	N	4.552	37.327	41.701	14.11
859	SER	CA	4.152	38.693	41.351	13.84
860	SER	C	2.681	38.899	41.621	14.27
861	SER	O	1.854	38.015	41.464	13.39
862	SER	CB	4.462	38.899	39.829	13.28
863	SER	OG	5.745	38.417	39.369	13.97
864	ARG	N	2.389	40.117	42.068	15.30
865	ARG	CA	1.022	40.497	42.358	15.25
866	ARG	C	0.390	41.239	41.189	14.31
867	ARG	O	-0.817	41.375	41.116	11.90
868	ARG	CB	1.055	41.352	43.620	16.01
869	ARG	CG	-0.333	41.453	44.243	21.04

870	ARG	CD	-0.934	42.809	43.980	23.71
871	ARG	NE	-1.985	43.095	44.935	25.68
872	ARG	CZ	-3.145	42.448	44.880	25.46
873	ARG	NH1	-3.278	41.374	44.164	22.79
874	ARG	NH2	-4.168	42.930	45.529	27.74
875	GLY	N	1.276	41.733	40.301	12.62
876	GLY	CA	0.899	42.673	39.263	10.16
877	GLY	C	1.631	42.376	37.956	10.24
878	GLY	O	2.792	41.984	37.944	9.74
879	VAL	N	0.909	42.597	36.861	10.10
880	VAL	CA	1.554	42.588	35.545	9.04
881	VAL	C	1.189	43.904	34.860	7.92
882	VAL	O	0.021	44.276	34.795	8.52
883	VAL	CB	0.955	41.434	34.717	7.21
884	VAL	CG1	0.741	40.059	35.377	10.00
885	VAL	CG2	1.208	41.428	33.216	6.46
886	VAL	N	2.225	44.560	34.356	6.18
887	VAL	CA	2.002	45.766	33.558	5.67
888	VAL	C	2.204	45.440	32.090	5.05
889	VAL	O	3.294	45.104	31.685	8.26
890	VAL	CB	2.942	46.867	34.051	4.27
891	VAL	CG1	2.627	47.146	35.522	5.59
892	VAL	CG2	2.821	48.193	33.311	5.52
893	MET	N	1.129	45.564	31.315	6.05
894	MET	CA	1.132	45.435	29.850	6.12
895	MET	C	1.159	46.791	29.168	5.90
896	MET	O	0.263	47.591	29.379	6.94
897	MET	CB	-0.222	44.895	29.428	6.49
898	MET	CG	-0.347	44.620	27.938	5.59
899	MET	SD	-1.592	43.356	27.620	10.50
900	MET	CE	-1.470	43.249	25.807	2.00
901	LEU	N	2.146	47.028	28.319	5.40
902	LEU	CA	2.242	48.428	27.799	5.78
903	LEU	C	1.866	48.558	26.299	7.49
904	LEU	O	2.091	49.581	25.666	7.99
905	LEU	CB	3.632	48.997	28.075	6.33
906	LEU	CG	3.952	49.053	29.593	8.42
907	LEU	CD1	3.064	50.026	30.390	6.57
908	LEU	CD2	5.400	49.460	29.834	5.25
909	ASN	N	1.336	47.445	25.747	6.12
910	ASN	CA	1.077	47.367	24.327	8.78
911	ASN	C	-0.348	46.840	24.026	10.77
912	ASN	O	-0.979	46.296	24.907	11.62
913	ASN	CB	2.125	46.458	23.685	10.20
914	ASN	CG	1.956	45.019	24.175	10.50
915	ASN	OD1	1.469	44.137	23.509	13.52
916	ASN	ND2	2.370	44.830	25.401	11.44
917	ARG	N	-0.798	46.974	22.777	12.13
918	ARG	CA	-1.993	46.274	22.315	12.77
919	ARG	C	-1.619	44.915	21.703	11.64
920	ARG	O	-0.553	44.743	21.149	13.53
921	ARG	CB	-2.716	47.222	21.340	15.99

922	ARG	CG	-3.045	48.546	22.066	23.40
923	ARG	CD	-4.252	49.313	21.496	32.56
924	ARG	NE	-4.304	49.380	20.020	44.25
925	ARG	CZ	-3.229	49.594	19.246	50.26
926	ARG	NH1	-2.041	49.756	19.777	51.39
927	ARG	NH2	-3.324	49.640	17.948	53.49
928	VAL	N	-2.522	43.925	21.780	11.90
929	VAL	CA	-2.168	42.689	21.057	13.18
930	VAL	C	-2.076	42.945	19.536	12.04
931	VAL	O	-1.410	42.208	18.850	12.44
932	VAL	CB	-3.314	41.697	21.330	14.90
933	VAL	CG1	-3.544	41.230	22.786	14.45
934	VAL	CG2	-3.739	40.733	20.196	13.17
935	MET	N	-2.781	43.975	19.030	13.86
936	MET	CA	-2.503	44.415	17.669	16.37
937	MET	C	-1.936	45.845	17.600	15.93
938	MET	O	-2.532	46.816	18.063	15.73
939	MET	CB	-3.734	44.308	16.776	19.13
940	MET	CG	-3.319	44.384	15.289	25.05
941	MET	SD	-4.505	43.645	14.175	30.99
942	MET	CE	-4.816	45.133	13.287	28.20
943	GLU	N	-0.776	45.915	16.938	15.17
944	GLU	CA	-0.179	47.200	16.644	16.14
945	GLU	C	0.459	47.173	15.260	18.85
946	GLU	O	1.028	46.175	14.830	20.26
947	GLU	CB	0.888	47.527	17.679	15.90
948	GLU	CG	0.407	47.344	19.109	17.76
949	GLU	CD	1.416	47.771	20.137	18.82
950	GLU	OE1	2.568	47.438	19.990	16.03
951	GLU	OE2	1.021	48.466	21.072	15.57
952	LYS	N	0.322	48.325	14.571	22.41
953	LYS	CA	0.947	48.444	13.227	23.76
954	LYS	C	0.631	47.250	12.303	21.76
955	LYS	O	1.464	46.702	11.599	21.77
956	LYS	CB	2.450	48.721	13.386	24.05
957	LYS	CG	2.681	50.181	13.822	23.31
958	LYS	CD	3.794	50.330	14.847	25.30
959	LYS	CE	4.085	51.801	15.113	28.40
960	LYS	NZ	2.832	52.557	15.212	27.38
961	GLY	N	-0.656	46.844	12.413	20.87
962	GLY	CA	-1.177	45.815	11.522	19.66
963	GLY	C	-0.875	44.362	11.919	19.12
964	GLY	O	-1.358	43.436	11.269	19.90
965	SER	N	-0.076	44.207	12.978	17.43
966	SER	CA	0.409	42.896	13.385	16.48
967	SER	C	0.010	42.558	14.786	15.10
968	SER	O	-0.199	43.426	15.622	15.11
969	SER	CB	1.956	42.955	13.330	18.82
970	SER	OG	2.476	43.387	12.036	30.66
971	LEU	N	-0.028	41.228	14.996	14.24
972	LEU	CA	-0.222	40.624	16.300	13.02
973	LEU	C	1.075	40.659	17.114	12.02

974	LEU	O	2.026	39.930	16.888	12.03
975	LEU	CB	-0.717	39.195	16.092	13.63
976	LEU	CG	-2.160	39.215	15.545	10.24
977	LEU	CD1	-3.226	40.017	16.301	10.97
978	LEU	CD2	-2.646	37.927	14.916	9.61
979	LYS	N	1.105	41.571	18.084	11.18
980	LYS	CA	2.290	41.882	18.858	8.96
981	LYS	C	2.390	41.095	20.161	7.30
982	LYS	O	3.376	41.101	20.884	6.49
983	LYS	CB	2.258	43.376	19.126	12.36
984	LYS	CG	2.527	44.152	17.844	14.52
985	LYS	CD	3.978	44.105	17.484	16.12
986	LYS	CE	4.345	44.924	16.271	20.42
987	LYS	NZ	5.804	45.081	16.202	23.02
988	CYS	N	1.319	40.356	20.402	6.54
989	CYS	CA	1.256	39.673	21.686	10.66
990	CYS	C	0.100	38.668	21.635	14.07
991	CYS	O	-0.882	38.889	20.936	18.36
992	CYS	CB	1.133	40.710	22.839	9.20
993	CYS	SG	0.873	40.094	24.504	5.00
994	ALA	N	0.214	37.548	22.367	13.71
995	ALA	CA	-0.970	36.706	22.498	11.28
996	ALA	C	-2.054	37.332	23.451	13.57
997	ALA	O	-1.787	38.061	24.405	13.87
998	ALA	CB	-0.506	35.347	22.988	5.96
999	GLN	N	-3.315	36.986	23.148	13.22
1000	GLN	CA	-4.355	37.267	24.134	11.86
1001	GLN	C	-4.194	36.315	25.338	9.90
1002	GLN	O	-4.748	35.227	25.329	8.51
1003	GLN	CB	-5.696	36.958	23.442	11.64
1004	GLN	CG	-6.901	37.307	24.331	12.96
1005	GLN	CD	-6.930	38.782	24.786	15.38
1006	GLN	OE1	-7.275	39.155	25.885	18.48
1007	GLN	NE2	-6.501	39.645	23.923	10.76
1008	TYR	N	-3.353	36.690	26.311	10.20
1009	TYR	CA	-2.959	35.652	27.305	11.34
1010	TYR	C	-3.874	35.622	28.587	10.00
1011	TYR	O	-3.692	34.809	29.480	12.22
1012	TYR	CB	-1.451	35.764	27.671	9.57
1013	TYR	CG	-1.092	37.093	28.295	10.61
1014	TYR	CD1	-1.112	37.261	29.674	11.35
1015	TYR	CD2	-0.748	38.189	27.492	10.24
1016	TYR	CE1	-0.865	38.489	30.277	10.01
1017	TYR	CE2	-0.500	39.429	28.066	8.22
1018	TYR	CZ	-0.564	39.588	29.448	8.65
1019	TYR	OH	-0.317	40.841	29.935	7.28
1020	TRP	N	-4.815	36.557	28.642	9.43
1021	TRP	CA	-5.714	36.690	29.792	10.16
1022	TRP	C	-7.175	36.690	29.287	10.75
1023	TRP	O	-7.442	37.154	28.187	8.67
1024	TRP	CB	-5.341	37.945	30.612	8.10
1025	TRP	CG	-5.788	39.222	29.929	8.50

1026	TRP	CD1	-6.970	39.931	30.199	9.41
1027	TRP	CD2	-5.138	39.917	28.835	8.04
1028	TRP	NE1	-7.089	40.994	29.356	8.02
1029	TRP	CE2	-5.979	41.032	28.508	8.86
1030	TRP	CE3	-3.990	39.680	28.138	6.23
1031	TRP	CZ2	-5.626	41.863	27.469	7.39
1032	TRP	CZ3	-3.641	40.518	27.068	8.40
1033	TRP	CH2	-4.457	41.614	26.747	8.65
1034	PRO	N	-8.137	36.145	30.127	11.94
1035	PRO	CA	-9.538	36.107	29.746	11.58
1036	PRO	C	10.158	37.512	29.637	14.25
1037	PRO	O	10.022	38.396	30.486	14.80
1038	PRO	CB	10.225	35.238	30.819	8.41
1039	PRO	CG	-9.311	35.278	32.027	5.08
1040	PRO	CD	-7.939	35.615	31.474	10.33
1041	GLN	N	10.892	37.626	28.524	15.45
1042	GLN	CA	11.657	38.851	28.328	18.38
1043	GLN	C	13.068	38.858	28.949	19.02
1044	GLN	O	13.747	39.861	28.892	20.54
1045	GLN	CB	11.682	39.166	26.841	20.69
1046	GLN	CG	10.255	39.453	26.327	27.58
1047	GLN	CD	10.336	39.675	24.835	28.97
1048	GLN	OE1	10.447	38.767	24.036	27.29
1049	GLN	NE2	10.375	40.949	24.506	28.60
1050	LYS	N	13.516	37.738	29.523	19.10
1051	LYS	CA	14.764	37.856	30.269	18.50
1052	LYS	C	14.946	36.717	31.217	15.91
1053	LYS	O	14.342	35.680	31.035	16.84
1054	LYS	CB	15.921	37.842	29.309	24.10
1055	LYS	CG	15.932	36.706	28.297	25.36
1056	LYS	CD	16.993	36.968	27.238	29.33
1057	LYS	CE	17.243	38.464	27.014	37.08
1058	LYS	NZ	18.344	38.699	26.095	42.94
1059	GLU	N	15.801	36.951	32.206	14.50
1060	GLU	CA	15.976	36.171	33.393	14.90
1061	GLU	C	16.338	34.709	33.088	18.20
1062	GLU	O	15.719	33.790	33.632	21.55
1063	GLU	CB	17.056	36.856	34.217	15.32
1064	GLU	CG	16.575	38.151	34.874	13.30
1065	GLU	CD	16.724	39.424	34.004	16.29
1066	GLU	OE1	16.616	39.376	32.782	16.80
1067	GLU	OE2	16.964	40.491	34.568	16.60
1068	GLU	N	17.317	34.475	32.183	19.29
1069	GLU	CA	17.820	33.133	31.855	19.57
1070	GLU	C	16.760	32.233	31.213	21.30
1071	GLU	O	16.888	31.007	31.232	20.15
1072	GLU	CB	18.964	33.205	30.827	18.63
1073	GLU	CG	19.852	34.414	31.027	16.44
1074	GLU	CD	19.393	35.654	30.276	16.06
1075	GLU	OE1	19.651	35.750	29.079	17.52
1076	GLU	OE2	18.763	36.522	30.864	15.56
1077	LYS	N	15.763	32.878	30.564	21.95

1078	LYS	CA	14.806	32.104	29.783	24.05
1079	LYS	C	13.376	32.240	30.376	24.41
1080	LYS	O	12.539	32.989	29.869	24.56
1081	LYS	CB	14.884	32.562	28.310	26.00
1082	LYS	CG	16.297	32.545	27.708	32.43
1083	LYS	CD	16.445	31.919	26.320	39.12
1084	LYS	CE	15.519	30.736	26.063	47.59
1085	LYS	NZ	16.271	29.672	25.392	51.15
1086	GLU	N	13.140	31.494	31.483	24.94
1087	GLU	CA	11.782	31.372	32.025	23.85
1088	GLU	C	10.831	30.682	31.032	20.25
1089	GLU	O	11.227	29.985	30.119	19.30
1090	GLU	CB	11.754	30.531	33.308	26.32
1091	GLU	CG	13.084	30.345	34.016	32.27
1092	GLU	CD	13.812	29.168	33.377	33.00
1093	GLU	OE1	13.258	28.077	33.359	32.06
1094	GLU	OE2	14.929	29.369	32.909	35.48
1095	MET	N	-9.550	30.894	31.280	17.49
1096	MET	CA	-8.526	30.188	30.550	15.38
1097	MET	C	-7.902	29.097	31.442	16.86
1098	MET	O	-7.471	29.361	32.554	18.95
1099	MET	CB	-7.489	31.239	30.146	12.45
1100	MET	CG	-8.055	32.218	29.122	11.06
1101	MET	SD	-6.888	33.465	28.615	15.30
1102	MET	CE	-5.835	32.442	27.602	13.48
1103	ILE	N	-7.819	27.879	30.942	15.12
1104	ILE	CA	-6.944	26.908	31.605	16.59
1105	ILE	C	-5.708	26.614	30.770	17.15
1106	ILE	O	-5.788	26.242	29.614	19.86
1107	ILE	CB	-7.708	25.631	31.971	18.08
1108	ILE	CG1	-8.632	25.919	33.163	23.46
1109	ILE	CG2	-6.764	24.493	32.352	17.34
1110	ILE	CD1	10.089	25.551	32.914	24.91
1111	PHE	N	-4.558	26.751	31.426	16.66
1112	PHE	CA	-3.307	26.461	30.755	16.55
1113	PHE	C	-2.838	25.024	31.123	19.38
1114	PHE	O	-2.330	24.746	32.201	19.28
1115	PHE	CB	-2.336	27.588	31.105	12.36
1116	PHE	CG	-2.824	28.944	30.818	10.57
1117	PHE	CD1	-2.749	29.439	29.534	8.04
1118	PHE	CD2	-3.334	29.723	31.855	11.55
1119	PHE	CE1	-3.201	30.723	29.284	10.42
1120	PHE	CE2	-3.787	31.007	31.608	11.87
1121	PHE	CZ	-3.719	31.506	30.311	12.28
1122	GLU	N	-3.116	24.104	30.205	21.82
1123	GLU	CA	-3.039	22.720	30.661	25.19
1124	GLU	C	-1.584	22.256	30.878	24.14
1125	GLU	O	-1.290	21.361	31.659	25.33
1126	GLU	CB	-3.639	21.787	29.605	31.07
1127	GLU	CG	-5.166	21.765	29.396	39.94
1128	GLU	CD	-5.454	20.639	28.364	48.24
1129	GLU	OE1	-5.364	20.905	27.164	52.05

1130	GLU	OE2	-5.724	19.507	28.772	51.99
1131	ASP	N	-0.697	22.914	30.136	23.00
1132	ASP	CA	0.712	22.482	30.155	22.21
1133	ASP	C	1.446	22.782	31.508	20.47
1134	ASP	O	2.261	22.031	32.033	19.77
1135	ASP	CB	1.332	23.130	28.915	21.00
1136	ASP	CG	1.430	24.643	29.079	22.61
1137	ASP	OD1	0.486	25.282	29.556	26.49
1138	ASP	OD2	2.454	25.190	28.734	21.60
1139	THR	N	1.068	23.914	32.079	19.14
1140	THR	CA	1.645	24.175	33.404	16.22
1141	THR	C	0.561	24.054	34.479	18.50
1142	THR	O	0.848	24.327	35.628	20.38
1143	THR	CB	2.051	25.710	33.412	14.66
1144	THR	OG1	0.989	26.641	33.065	13.92
1145	THR	CG2	3.261	25.983	32.480	11.30
1146	ASN	N	-0.686	23.637	34.105	19.33
1147	ASN	CA	-1.730	23.331	35.094	19.95
1148	ASN	C	-2.154	24.539	35.987	21.85
1149	ASN	O	-2.161	24.482	37.214	22.33
1150	ASN	CB	-1.180	22.269	36.021	24.72
1151	ASN	CG	-2.334	21.494	36.646	27.53
1152	ASN	OD1	-3.342	21.190	36.060	30.68
1153	ASN	ND2	-2.193	21.200	37.881	26.04
1154	LEU	N	-2.484	25.635	35.297	22.78
1155	LEU	CA	-2.886	26.899	35.936	22.24
1156	LEU	C	-4.265	27.315	35.376	22.59
1157	LEU	O	-4.561	27.167	34.194	23.95
1158	LEU	CB	-1.875	28.025	35.599	21.01
1159	LEU	CG	-0.701	28.404	36.548	17.04
1160	LEU	CD1	0.610	28.303	35.804	13.07
1161	LEU	CD2	-0.612	27.764	37.930	14.04
1162	LYS	N	-5.087	27.901	36.222	20.53
1163	LYS	CA	-6.322	28.485	35.725	17.91
1164	LYS	C	-6.339	30.003	35.942	17.68
1165	LYS	O	-5.903	30.515	36.958	16.29
1166	LYS	CB	-7.441	27.691	36.368	17.25
1167	LYS	CG	-8.807	28.050	35.869	18.58
1168	LYS	CD	-9.895	27.178	36.443	22.19
1169	LYS	CE	11.140	27.885	36.932	22.34
1170	LYS	NZ	11.879	26.984	37.836	24.46
1171	LEU	N	-6.846	30.705	34.934	17.39
1172	LEU	CA	-7.006	32.157	34.943	15.35
1173	LEU	C	-8.477	32.621	34.637	16.31
1174	LEU	O	-9.075	32.259	33.636	16.43
1175	LEU	CB	-5.961	32.752	34.009	12.86
1176	LEU	CG	-5.853	34.284	34.126	9.27
1177	LEU	CD1	-5.021	34.787	32.956	8.45
1178	LEU	CD2	-5.200	34.687	35.454	9.53
1179	THR	N	-9.012	33.479	35.526	13.25
1180	THR	CA	10.363	34.063	35.463	12.10
1181	THR	C	10.355	35.563	35.597	13.46

1182	THR	O	-9.718	36.088	36.499	15.11
1183	THR	CB	11.097	33.461	36.694	12.89
1184	THR	OG1	10.946	32.013	36.745	11.16
1185	THR	CG2	12.589	33.673	36.530	13.73
1186	LEU	N	11.097	36.253	34.707	12.69
1187	LEU	CA	11.361	37.680	34.900	13.21
1188	LEU	C	12.268	37.840	36.109	16.36
1189	LEU	O	13.383	37.337	36.138	17.33
1190	LEU	CB	12.105	38.280	33.697	9.27
1191	LEU	CG	12.355	39.790	33.774	5.96
1192	LEU	CD1	13.113	40.189	32.520	3.05
1193	LEU	CD2	11.034	40.574	33.866	2.04
1194	ILE	N	11.767	38.531	37.113	16.98
1195	ILE	CA	12.711	38.814	38.209	16.56
1196	ILE	C	13.488	40.095	37.970	15.67
1197	ILE	O	14.677	40.183	38.224	16.31
1198	ILE	CB	12.058	38.673	39.567	14.46
1199	ILE	CG1	11.521	37.227	39.718	13.21
1200	ILE	CG2	13.057	39.124	40.658	11.57
1201	ILE	CD1	12.570	36.104	39.539	7.88
1202	SER	N	12.769	41.053	37.410	16.03
1203	SER	CA	13.492	42.181	36.859	17.37
1204	SER	C	12.449	43.133	36.298	19.23
1205	SER	O	11.276	42.946	36.557	19.21
1206	SER	CB	14.107	42.990	38.027	20.04
1207	SER	OG	13.123	43.511	39.003	20.18
1208	GLU	N	12.886	44.193	35.634	22.29
1209	GLU	CA	11.982	45.230	35.140	23.93
1210	GLU	C	12.557	46.663	35.235	23.31
1211	GLU	O	13.754	46.861	35.283	27.00
1212	GLU	CB	11.701	44.924	33.697	24.38
1213	GLU	CG	12.961	44.717	32.896	25.56
1214	GLU	CD	12.581	44.588	31.426	31.45
1215	GLU	OE1	11.402	44.721	31.054	32.20
1216	GLU	OE2	13.483	44.345	30.651	36.07
1217	ASP	N	11.671	47.634	35.279	21.18
1218	ASP	CA	11.995	49.030	35.441	17.82
1219	ASP	C	11.395	49.764	34.225	18.72
1220	ASP	O	10.200	50.051	34.108	20.93
1221	ASP	CB	11.443	49.430	36.814	22.34
1222	ASP	CG	11.406	50.932	37.034	28.58
1223	ASP	OD1	12.354	51.602	36.636	27.70
1224	ASP	OD2	10.412	51.436	37.597	33.90
1225	ILE	N	12.306	49.980	33.282	18.31
1226	ILE	CA	11.933	50.554	32.008	19.98
1227	ILE	C	11.874	52.099	32.025	20.84
1228	ILE	O	12.850	52.781	32.267	20.15
1229	ILE	CB	12.946	50.053	30.978	20.01
1230	ILE	CG1	12.853	48.540	30.856	20.02
1231	ILE	CG2	12.762	50.696	29.607	19.35
1232	ILE	CD1	13.722	47.987	29.733	21.08
1233	LYS	N	10.700	52.617	31.682	22.09

1234	LYS	CA	10.548	54.069	31.550	21.26
1235	LYS	C	10.289	54.430	30.108	20.78
1236	LYS	O	10.038	53.563	29.266	22.79
1237	LYS	CB	-9.402	54.433	32.459	22.27
1238	LYS	CG	-9.721	54.009	33.868	22.36
1239	LYS	CD	10.326	55.177	34.630	25.91
1240	LYS	CE	10.825	54.813	36.002	28.42
1241	LYS	NZ	11.309	56.052	36.589	30.51
1242	THR	N	10.327	55.686	29.733	19.62
1243	THR	CA	10.249	56.059	28.237	20.98
1244	THR	C	-8.822	55.510	27.732	20.84
1245	THR	O	-8.780	55.122	26.657	22.93
1246	THR	CB	-9.822	57.568	28.309	19.41
1247	THR	OG1	-8.833	57.806	29.314	22.97
1248	THR	CG2	11.069	58.348	28.636	24.19
1249	TYR	N	-7.719	55.518	28.646	20.25
1250	TYR	CA	-6.458	55.219	28.007	18.72
1251	TYR	C	-5.770	53.922	28.602	18.44
1252	TYR	O	-4.685	53.476	28.203	20.29
1253	TYR	CB	-5.607	56.494	28.042	16.14
1254	TYR	CG	-4.897	56.888	29.314	13.33
1255	TYR	CD1	-5.465	57.864	30.081	14.09
1256	TYR	CD2	-3.682	56.427	29.721	13.30
1257	TYR	CE1	-5.016	58.191	31.311	17.45
1258	TYR	CE2	-3.090	56.866	30.874	19.22
1259	TYR	CZ	-3.767	57.715	31.696	19.65
1260	TYR	OH	-3.079	58.078	32.801	20.24
1261	TYR	N	-6.461	53.351	29.591	15.06
1262	TYR	CA	-5.915	52.151	30.228	14.61
1263	TYR	C	-7.010	51.388	30.962	15.66
1264	TYR	O	-8.023	51.956	31.320	17.43
1265	TYR	CB	-4.719	52.522	31.134	15.82
1266	TYR	CG	-5.118	53.115	32.443	19.10
1267	TYR	CD1	-5.449	52.289	33.528	21.07
1268	TYR	CD2	-5.158	54.491	32.606	21.69
1269	TYR	CE1	-5.830	52.813	34.755	19.08
1270	TYR	CE2	-5.580	55.003	33.823	22.03
1271	TYR	CZ	-5.883	54.185	34.902	20.70
1272	TYR	OH	-6.221	54.746	36.125	20.35
1273	THR	N	-6.777	50.103	31.213	13.79
1274	THR	CA	-7.774	49.326	31.968	14.01
1275	THR	C	-7.068	48.551	33.024	13.51
1276	THR	O	-6.050	47.935	32.736	12.55
1277	THR	CB	-8.369	48.336	30.922	15.24
1278	THR	OG1	-9.115	48.941	29.853	15.88
1279	THR	CG2	-9.278	47.291	31.615	12.04
1280	VAL	N	-7.636	48.525	34.247	13.29
1281	VAL	CA	-7.079	47.585	35.204	14.30
1282	VAL	C	-8.024	46.398	35.369	14.29
1283	VAL	O	-9.217	46.546	35.469	15.36
1284	VAL	CB	-6.887	48.311	36.548	13.88
1285	VAL	CG1	-6.372	49.756	36.536	8.84

1286	VAL	CG2	-6.537	47.465	37.788	13.68
1287	ARG	N	-7.465	45.214	35.420	12.81
1288	ARG	CA	-8.229	44.025	35.644	11.72
1289	ARG	C	-7.772	43.342	36.930	12.76
1290	ARG	O	-6.620	43.342	37.320	12.68
1291	ARG	CB	-8.045	43.128	34.450	11.12
1292	ARG	CG	-8.286	43.859	33.139	15.30
1293	ARG	CD	-8.261	42.904	31.963	20.03
1294	ARG	NE	-8.786	43.590	30.765	23.64
1295	ARG	CZ	-7.985	44.278	29.965	22.07
1296	ARG	NH1	-6.692	44.288	30.189	21.13
1297	ARG	NH2	-8.468	44.954	28.976	24.55
1298	GLN	N	-8.730	42.732	37.569	15.02
1299	GLN	CA	-8.427	41.791	38.595	17.49
1300	GLN	C	-8.600	40.390	38.060	15.96
1301	GLN	O	-9.647	40.036	37.541	14.32
1302	GLN	CB	-9.382	42.030	39.713	22.81
1303	GLN	CG	-9.262	41.053	40.854	32.87
1304	GLN	CD	10.405	41.347	41.813	39.46
1305	GLN	OE1	11.408	41.967	41.482	41.19
1306	GLN	NE2	10.187	40.875	43.013	42.57
1307	LEU	N	-7.538	39.630	38.194	15.65
1308	LEU	CA	-7.498	38.264	37.718	15.53
1309	LEU	C	-7.483	37.312	38.917	15.62
1310	LEU	O	-7.009	37.654	39.984	17.25
1311	LEU	CB	-6.202	38.112	36.903	16.62
1312	LEU	CG	-6.242	38.575	35.434	14.27
1313	LEU	CD1	-4.942	38.991	34.790	16.50
1314	LEU	CD2	-7.496	39.201	34.857	12.30
1315	GLU	N	-7.982	36.101	38.711	15.87
1316	GLU	CA	-7.649	35.059	39.670	14.28
1317	GLU	C	-6.819	34.006	38.952	12.82
1318	GLU	O	-7.183	33.521	37.900	11.62
1319	GLU	CB	-8.912	34.480	40.323	15.74
1320	GLU	CG	-8.504	33.348	41.273	20.52
1321	GLU	CD	-9.616	32.843	42.174	22.26
1322	GLU	OE1	10.040	33.589	43.047	26.87
1323	GLU	OE2	10.020	31.708	42.012	16.51
1324	LEU	N	-5.679	33.708	39.578	13.74
1325	LEU	CA	-4.780	32.673	39.137	14.23
1326	LEU	C	-4.851	31.471	40.119	16.97
1327	LEU	O	-4.491	31.577	41.289	13.98
1328	LEU	CB	-3.391	33.307	39.131	13.18
1329	LEU	CG	-2.359	32.718	38.152	14.58
1330	LEU	CD1	-2.685	31.494	37.300	13.64
1331	LEU	CD2	-0.889	32.995	38.428	15.94
1332	GLU	N	-5.312	30.327	39.601	18.45
1333	GLU	CA	-5.299	29.116	40.366	18.22
1334	GLU	C	-4.243	28.118	39.888	19.24
1335	GLU	O	-4.250	27.596	38.789	17.31
1336	GLU	CB	-6.667	28.458	40.354	18.17
1337	GLU	CG	-6.781	27.377	41.470	20.37

1338	GLU	CD	-8.058	26.570	41.332	22.37
1339	GLU	OE1	-8.995	26.977	40.666	21.04
1340	GLU	OE2	-8.108	25.474	41.879	25.85
1341	ASN	N	-3.345	27.828	40.804	22.37
1342	ASN	CA	-2.546	26.649	40.584	25.92
1343	ASN	C	-3.387	25.377	40.755	25.53
1344	ASN	O	-3.572	24.897	41.861	25.67
1345	ASN	CB	-1.325	26.765	41.500	27.66
1346	ASN	CG	-0.601	25.427	41.717	27.77
1347	ASN	OD1	-1.077	24.341	41.436	27.56
1348	ASN	ND2	0.571	25.533	42.244	29.56
1349	LEU	N	-3.807	24.821	39.627	23.83
1350	LEU	CA	-4.652	23.629	39.641	22.45
1351	LEU	C	-4.106	22.430	40.435	24.96
1352	LEU	O	-4.848	21.603	40.937	26.15
1353	LEU	CB	-4.919	23.245	38.197	16.54
1354	LEU	CG	-6.200	23.824	37.584	15.77
1355	LEU	CD1	-6.355	23.781	36.061	13.72
1356	LEU	CD2	-6.966	24.930	38.291	12.99
1357	THR	N	-2.783	22.364	40.547	26.74
1358	THR	CA	-2.184	21.257	41.276	27.87
1359	THR	C	-2.387	21.269	42.779	29.27
1360	THR	O	-2.324	20.235	43.438	30.62
1361	THR	CB	-0.656	21.271	40.960	28.76
1362	THR	OG1	-0.222	21.276	39.580	28.70
1363	THR	CG2	0.076	20.197	41.798	28.43
1364	THR	N	-2.626	22.437	43.328	28.69
1365	THR	CA	-2.904	22.402	44.775	28.99
1366	THR	C	-4.201	23.179	45.033	32.17
1367	THR	O	-4.673	23.210	46.146	34.29
1368	THR	CB	-1.808	23.352	45.374	25.58
1369	THR	OG1	-1.906	24.712	44.893	24.80
1370	THR	CG2	-0.413	22.844	44.960	21.97
1371	GLN	N	-4.726	23.838	43.975	34.19
1372	GLN	CA	-5.903	24.683	44.149	36.02
1373	GLN	C	-5.651	25.904	45.068	34.54
1374	GLN	O	-6.560	26.502	45.630	34.82
1375	GLN	CB	-7.056	23.797	44.633	40.16
1376	GLN	CG	-7.447	22.737	43.605	46.76
1377	GLN	CD	-8.777	22.111	44.000	50.73
1378	GLN	OE1	-9.050	21.806	45.145	50.25
1379	GLN	NE2	-9.586	21.893	42.985	53.71
1380	GLU	N	-4.364	26.264	45.184	33.22
1381	GLU	CA	-4.084	27.590	45.723	33.18
1382	GLU	C	-4.526	28.672	44.740	30.34
1383	GLU	O	-4.574	28.507	43.524	28.93
1384	GLU	CB	-2.597	27.807	45.960	37.35
1385	GLU	CG	-2.029	27.073	47.151	45.79
1386	GLU	CD	-0.503	27.118	47.092	53.23
1387	GLU	OE1	0.090	28.186	47.253	54.41
1388	GLU	OE2	0.110	26.083	46.854	58.44

1389	THR	N	-4.771	29.824	45.341	27.29
1390	THR	CA	-5.321	30.882	44.519	21.75
1391	THR	C	-4.702	32.231	44.866	20.39
1392	THR	O	-4.480	32.572	46.024	21.88
1393	THR	CB	-6.901	30.855	44.831	20.91
1394	THR	OG1	-7.887	30.317	43.926	18.30
1395	THR	CG2	-7.402	32.239	45.242	22.13
1396	ARG	N	-4.478	33.010	43.805	17.74
1397	ARG	CA	-3.917	34.344	44.023	15.94
1398	ARG	C	-4.593	35.365	43.131	15.58
1399	ARG	O	-4.922	35.078	41.994	14.33
1400	ARG	CB	-2.434	34.314	43.653	16.13
1401	ARG	CG	-1.673	33.304	44.487	18.13
1402	ARG	CD	-0.197	33.503	44.382	18.87
1403	ARG	NE	0.471	32.485	45.132	20.71
1404	ARG	CZ	1.666	32.149	44.780	21.27
1405	ARG	NH1	2.351	32.800	43.866	19.60
1406	ARG	NH2	2.163	31.120	45.349	22.46
1407	GLU	N	-4.737	36.564	43.664	16.20
1408	GLU	CA	-5.232	37.648	42.820	17.96
1409	GLU	C	-4.066	38.466	42.226	18.25
1410	GLU	O	-3.223	39.023	42.925	19.75
1411	GLU	CB	-6.054	38.623	43.649	20.78
1412	GLU	CG	-6.513	39.851	42.845	23.52
1413	GLU	CD	-6.777	40.984	43.840	31.18
1414	GLU	OE1	-5.867	41.331	44.491	35.95
1415	GLU	OE2	-7.849	41.495	43.990	33.07
1416	ILE	N	-4.131	38.557	40.902	16.64
1417	ILE	CA	-3.169	39.310	40.109	12.04
1418	ILE	C	-3.880	40.515	39.527	11.07
1419	ILE	O	-4.862	40.403	38.819	11.62
1420	ILE	CB	-2.704	38.444	38.926	9.49
1421	ILE	CG1	-2.292	37.027	39.359	8.19
1422	ILE	CG2	-1.679	39.155	38.027	6.71
1423	ILE	CD1	-1.062	36.953	40.271	8.86
1424	LEU	N	-3.314	41.663	39.796	12.20
1425	LEU	CA	-3.765	42.894	39.153	11.34
1426	LEU	C	-3.068	43.084	37.797	10.98
1427	LEU	O	-1.855	43.017	37.679	11.20
1428	LEU	CB	-3.376	43.996	40.135	11.87
1429	LEU	CG	-4.459	44.428	41.136	14.45
1430	LEU	CD1	-3.851	45.049	42.374	13.48
1431	LEU	CD2	-5.510	43.382	41.494	14.58
1432	HIS	N	-3.887	43.335	36.774	11.21
1433	HIS	CA	-3.409	43.599	35.405	10.35
1434	HIS	C	-3.599	45.056	35.037	11.82
1435	HIS	O	-4.720	45.529	34.960	13.04
1436	HIS	CB	-4.223	42.719	34.475	10.25
1437	HIS	CG	-3.735	42.604	33.061	5.26
1438	HIS	ND1	-4.371	43.183	32.017	4.31
1439	HIS	CD2	-2.622	41.907	32.605	3.49
1440	HIS	CE1	-3.660	42.851	30.935	4.28